

Stem Cells: A Reformist Therapeutic Approach to Orthopaedic Sports Medicine

Onur ORAL^{1,*}, George NOMIKOS², Nikitas NOMIKOS^{3,4}

¹Ege University, Faculty of Sports Sciences, Izmir, Turkey

²Chios Hospital, Department of Orthopaedic Surgery, Chios, Greece

³School of Physical Education & Sport Science, National & Kapodistrian University of Athens

⁴Medical School, National & Kapodistrian University of Athens

*Corresponding author: onur.oral@ege.edu.tr

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Abstract Background: The aim of the research is to identify, study the effects of stem cell therapies on sports injuries and examine how stem cell therapies may benefit the healing process and improve the athletes' physical state. With an extensive literature review, the purpose of this article to investigate the true potentials of regenerative stem cell therapy and shed light on innovative ways of treatment for sports injuries. It is theorized that stem cell therapy is an efficient and effective treatment method for sports injuries. Stem cell therapy is an innovative way of treating musculoskeletal injuries to provide faster and safer treatment to athletes. As sports injuries are one of the major concerns of the athletes, stem cell therapies are quite promising with effective and safe results. It is possible to fully heal certain injuries, regain functions, and reduce symptoms. Stem cell therapy is a method that should be popularised and preferred particularly by athletes.

Keywords: stem cell, musculoskeletal injuries, sport injury

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1. Introduction

In the past years, the interest in therapeutic use of stem cells in the world of sports has gained quite significance. This interest does not include the field of medicine only but also includes the media as well. Recently, news about elite athletes who prefer stem cell therapies is seen commonly in the press on a global extent [1]. For instance, it is known that elite and professional athletes such as footballers and baseballers from national leagues benefit from going outside the country and receiving stem cell therapies for sports injuries [2,3].

The reason why stem cells are in the sight of science and sports is that they have very unique features and because of that stem cells offer great potentials in terms of therapeutic medicine. Injuries affect human lives physically, mentally and socially. For instance, according to the data of 2005, 1 out of 10 people are known to have a musculoskeletal injury in the US. Because of these injuries, the number of workdays skipped is equal to almost 72 million, which is a great amount [4]. As for athletes, the risk of being injured is even higher and the further effects can be more serious. When athletes are injured, they have economic, carer costs; finally they can even lose their physical potential if the injury is not healed fully. Yet, as the world of medicine progresses, there are

new treatment methods and stem cell therapy is a pioneering method for healing injuries.

1.1. Definition and Types

The type of cells that have the capability of developing into various types of cells and tissues are called *stem cells*. This wide variety of tissues includes muscle, bone, nerve tissues [5]. It is widely approved that stem cells have the great potential to cure and avoid many health problems [6-16]. Stem cells can stay passive till they are excited, transform into several types of tissues and renew themselves [17,18]. They offer the chance to relocate the damaged cells with new ones. For this reason, the issue of using stem cells for therapeutic purposes is a great interest in the world of medicine.

There are three types of stem cells: embryonic stem cells, adult stem cells, umbilical cord blood stem cells. Stem cells mainly come from bone marrow and placenta [19].

1.1.1. Mesenchymal Stem Cells (MSCs)

MSCs have particularly gained the interest of the medical community. This type of stem cells can transform into different types of tissue cells such as tendon tissue, adipose tissue, muscle tissue, etc [20,21,22,23]. Bone marrow is one of the main sources of MSCs. After obtaining the cells, they are put into culture. One of the most beneficial aspects of these types of cells is that they

can easily be obtained from adult tissues and thus there is no problem of ethics [24].

Nearly all tissues in the human body include MSCs. They can also be obtained from adipose tissue, umbilical cord, fetal liver, etc. [25,26,27].

1.2. Sport Injuries

Stem cell therapies are used in a wide extent of health issues. From orthopaedic injuries to hair transplantation and skin regeneration, stem cells offer very unique solutions. For athletes, as it is the statement of this study, sports injuries which are one of the main concerns of any athlete can be efficiently treated with stem cells. Several studies examined stem cell therapy in the context of sports injuries. The most common injury types are ligaments, bones, muscles, and tendons.

1.2.1. Ligament Injury

One of the at-risk body parts of athletes is ligament. Ligament, also known as connective tissue, is open to sports injuries. In addition, the healing process is quite slow and compelling.

1.2.2. Bone Injury

Bone injuries are one of the main concerns of athletes. Athletes often get their bones fractured and cannot perform fully until they are completely healed. With the use of stem cell therapy, athletes' healing process may be improved. Thus, they can continue their career safely.

1.2.3. Muscle Injury

Treatment of muscle injuries is difficult. These types of sports injuries may even require surgeries to get fully healed.

1.3. Mechanism of Stem Cell Therapy

In stem cell therapy, which is included in the category of regenerative medicine, five main steps may be stated. Firstly, the cells which are obtained from the patient's body are put into culture. The cells are injected into the wounded area. Afterward, stem cells are expected to adapt. These cells locate themselves in the zone where the injury is present. In this zone, they acclimatize. Then, these cells reproduce and specialize in the cell type which is determined by the organism. Lastly, these new cells replace the injured cells to heal the tissue.

2. Discussion

In their article Chong et al., stem cells were used for the purpose to heal the tendon. BM-MSC fibrin gel and simple fibrin gel were used on rabbits' Achilles tendon. It was aimed to investigate the influence of BM-MSC fibrin gel. After 3 weeks, the results demonstrated an increase of 32% in modulus of elasticity. In addition, the percentage of I-type collagen fibers changed positively [28].

Another research was conducted on Achilles tendon of rabbits. PLGA scaffolds were cultured using BM-MSC

and simple scaffold. After the therapy, it was observed that the study group that received BM-MSC showed better levels in the generation of new tissues. This subject group's modulus of elasticity was estimated at 62,6%. Tensile strength was estimated to be 87%. These results concluded that for the repairment of Achilles tendon, BM-MSC's effect has a long duration. [29].

In a study by Silva et al., it was observed that among the 43 patients chosen for the study, the BM-MSCs amount which is required for the regeneration of Anterior cruciate ligament were restricted to a certain level [30]. Another research was conducted on rats to understand the potential therapeutic effect of stem cells for ACL regeneration. In the study, stromal mesenchymal cells were used. The study concluded that ligament injuries are likely to be treated with the help of stem cells [31]. MSCs were used in another study with an additional substance, collagen type 1. The study suggested that these two substances together form a good therapy alternative for sports-related ligament injuries [32].

Vanini et al. used MSC as a therapy for the treatment of talus lesions of 140 athletes. After the treatment process, the study concluded that MSC therapy was quite successful and allowed the athletes to continue their sports lives without any problems [33].

Sheyn et al. focused on stem cell therapies on bones. According to the research, pigs were used as animal subjects and were divided into two groups. On one group, adipose-derived stem cells were used to assess the effect on bones. The results demonstrated a meaningful improvement in the formation of bone and the process of healing for the group of animals that received stem cell treatment. The bone formation process was found to be half the time of the non-stem cell group [34].

Centeno et al. studied patients with osteoarthritis in the knees and hips. After stem cell treatment, the patients were taken into an MRI. As the results demonstrated, cartilage has become thicker than before. Also, bone spurs issue showed significant improvement in patients with hip osteoarthritis, 4 weeks post-MSCs treatment. Furthermore, meniscus and cartilage were found to be thicker in 6 months [35].

The research analyzed stem cell therapy's influence on muscle injuries. Ota et al. used muscle-derived stem cells to treat bruised muscle. The study was conducted on mice. Researchers set 3 groups and transplanted the cells at one, four and seven days. At the end of 2 weeks, VEGF was observed to be increased and muscles were strengthened with the group that received the transplantation at day 4. The 7th-day group also demonstrated improvements. The study stated that with the help of stem cell therapy, the recovery process can be faster [36].

The healing rates showed variations in a mice study. Meniscal injuries of mice were treated with MSC. Animal groups were treated with fibrin glue and MSC and just fibrin glue. 3rd group received none of these treatments. The non-treated group showed no improvements. 28 subjects were included in the MSC-fibrin glue group. 21 subjects of his group showed positive progress while 2 showed no improvement. The rest demonstrated improvements but did not show a full recovery [37,38,39].

3. Conclusion

In summary, regenerative medicine and stem cell therapy is an innovative and effective method for the treatment of sports injuries of various types. Regarding our extensive literature review, there is evidence that stem cell therapies were able to heal musculoskeletal injuries, reduce pain and symptoms and regain functions. It is particularly interesting and important to emphasize the non-aggressive content of this method. Stem cell therapies offer an alternative to surgical treatments and complications. As sports injuries are one of the major concerns of the athletes, stem cell therapies are quite promising with effective, fast and safe results. For this reason, it is the statement of this study that stem cell therapy is a method that should be popularised and preferred particularly by athletes. The true potential and promises of this method's use in sports are to be further studied and investigation of optimized strategies is suggested.

References

- [1] Ajibade, D.A., Vance, D.D., Hare, J.M., Kaplan, L.D., Lesniak, B.P. (2014) Emerging Applications of Stem Cell and Regenerative Medicine to Sports Injuries. *Orthop J Sports Med.* 2014 Feb 6; 2(2): 2325967113519935.
- [2] Franklin, D. (2013). A dangerous game. *Sci Am*; 308(2): 27-28.
- [3] Pennington, B. (2007). For Athletes, the Next Fountain of Youth? *The New York Times*.
- [4] Bone and Joint Initiative. (2008). *The Burden of Musculoskeletal Diseases in the United States: Prevalence, Societal and Economic Cost.* Rosemont, IL: American Association for Orthopaedic Surgeons.
- [5] Nae, S., Bordeianu, I., Stancioiu, A. T., & Antohi, N. (2013). Human adipose-derived stem cells: Definition, isolation, tissue-engineering applications. *Romanian Journal of Morphology and Embryology*, 54(4), 919-924.
- [6] de Lazaro, I., Yilmazer, A., & Kostarelos, K. (2014). Induced pluripotent stem (iPS) cells: A new source for cell-based therapeutics? *Journal of Controlled Release*, 185, 37-44.
- [7] Ardashiry Lajimi, A., Hagh, M. F., Saki, N., Mortaz, E., Soleimani, M., & Rahim, F. (2013). Feasibility of cell therapy in multiple sclerosis: A systematic review of 83 studies. *International Journal of Hematology-Oncology and Stem Cell Research*, 7(1), 15-33.
- [8] Azizidoost, S., Bavarsad, M. S., Bavarsad, M. S., Shahrabi, S., Jaseb, K., Rahim, F., Shahjehani, M., Saba, F., Ghorbani, M., & Saki, N. (2015). The role of notch signaling in bone marrow niche. *Hematology*, 20(2), 93-103.
- [9] Dehghanifard, A., Shahjehani, M., Galehdari, H., Rahim, F., Hamid, F., Jaseb, K., Asnafi, A. A., Jalalifar, M. A., & Saki, N. (2013). Prenatal diagnosis of different polymorphisms of beta-globin gene in Ahvaz. *International Journal of Hematology-Oncology and Stem Cell Research*, 7(2), 17-22.
- [10] Ebrahimi, A., & Rahim, F. (2014). Recent immunomodulatory strategies in transplantation. *Immunological Investigations*, 43(8), 829-837.
- [11] Ebrahimi, A., Hosseini, S. A., & Rahim, F. (2014). Immunosuppressive therapy in allograft transplantation: From novel insights and strategies to tolerance and challenges. *Central-European Journal of Immunology*, 39(3), 400-409.
- [12] Rahim, F., Allahmoradi, H., Salari, F., Shahjehani, M., Fard, A. D., Hosseini, S. A., & Mousakhani, H. (2013). Evaluation of signaling pathways involved in gamma-globin gene induction using fetal hemoglobin inducer drugs. *International Journal of Hematology-Oncology and Stem Cell Research*, 7(3), 41-46.
- [13] Saeidi, S., Jaseb, K., Asnafi, A. A., Rahim, F., Pourmotahari, F., Mardaniyan, S., Yousefi, H., Alghasi, A., Shahjehani, M., & Saki, N. (2014). Immune thrombocytopenic Purpura in children and adults: A comparative retrospective study in IRAN. *International Journal of Hematology-Oncology and Stem Cell Research*, 8(3), 30-36.
- [14] Saki, N., Jalalifar, M. A., Soleimani, M., Hajizamani, S., & Rahim, F. (2013). Adverse effect of high glucose concentration on stem cell therapy. *International Journal of Hematology-Oncology and Stem Cell Research*, 7(3), 34-40.
- [15] Shahrabi, S., Azizidoost, S., Shahjehani, M., Rahim, F., Ahmadzadeh, A., & Saki, N. (2014). New insights in cellular and molecular aspects of BM niche in chronic myelogenous leukemia. *Tumour Biology*, 35(11), 10627-10633.
- [16] Rahim, S., Rahim, F., Shirbandi, K., Haghghi, B.B., Arjmand, B. (2018) Sports Injuries: Diagnosis, Prevention, Stem Cell Therapy, and Medical Sport Strategy. In: Pham P. (eds) *Tissue Engineering and Regenerative Medicine. Advances in Experimental Medicine and Biology*, vol 1084. Springer, Cham.
- [17] Årøen, A. (2011). Stem cell therapy for articular cartilage defects. *British medical bulletin*, 99(1), 227.
- [18] Awad, H.A., Halvorsen, Y.D., Gimble, J.M., Guilak, F. (2003). Effects of transforming growth factor beta1 and dexamethasone on the growth and chondrogenic differentiation of adipose-derived stromal cells. *Tissue Eng*; 9:1301-1312.
- [19] Markoulaki, S., Meissner, A., & Jaenisch, R. (2008). Somatic cell nuclear transfer and derivation of embryonic stem cells in the mouse. *Methods*, 45(2), 101-114.
- [20] Barry, F., Boynton, R.E., Liu, B., Murphy, J.M. (2001). Chondrogenic differentiation of mesenchymal stem cells from bone marrow: differentiation-dependent gene expression of matrix components. *Exp Cell Res*; 268: 189- 200.
- [21] Colter, D.C., Sekiya, I., Prockop, D.J. (2001). Identification of a subpopulation of rapidly self-renewing and multipotential adult stem cells in colonies of human marrow stromal cells. *Proc Natl Acad Sci U S A*; 98: 7841-5.
- [22] Pittenger, M.F., Mackay, A.M., Beck, S.C., Jaiswal, R.K., Douglas, R., Mosca, J.D., et al. (1999). Multilineage potential of adult human mesenchymal stem cells. *Science*; 284: 143-7.
- [23] Toma, C., Pittenger, M.F., Cahill, K.S., Byrne, B.J., Kessler, P.D. (2002). Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. *Circulation*; 105: 93- 8.
- [24] Murphy, J.M., Fink, D.J., Hunziker, E.B., Barry, F.P. (2003). Stem cell therapy in a caprine model of osteoarthritis.
- [25] Anjos-Afonso, F., Bonnet, D. (2007). Nonhematopoietic/ endothelial SSEA-1⁺ cells define the most primitive progenitors in the adult murine bone marrow mesenchymal compartment. *Blood*; 109: 1298-306.
- [26] Bianco, P., Robey, P.G., Simmons, P.J. (2008). Mesenchymal stem cells: revisiting history, concepts, and assays. *Cell Stem Cell*; 2: 313-9.
- [27] In't Anker, P.S., Scherjon, S.A., Kleijburg-van der Keur, C., de Groot-Swings, G.M., Claas, F.H., Fibbe, W.E., et al. Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. *Stem Cells* 2004; 22: 1338-45.
- [28] Chong, A.K., Ang, A.D., Goh, J.C., Hui, J.H., Lim, A.Y., Lee, E.H., & Lim, B.H. (2007). Bone marrow-derived mesenchymal stem cells influence early tendon-healing in a rabbit achilles tendon model. *The Journal of Bone and Joint Surgery. American Volume*, 89(1), 74-81.
- [29] Ouyang, H.W., Goh, J.C., Thambyah, A., Teoh, S. H., & Lee, E. H. (2003). Knitted poly-lactide-co-glycolide scaffold loaded with bone marrow stromal cells in repair and regeneration of rabbit Achilles tendon. *Tissue Engineering*, 9(3), 431-439.
- [30] Silva, A., Sampaio, R., Fernandes, R., & Pinto, E. (2014). Is there a role for adult non-cultivated bone marrow stem cells in ACL reconstruction? *Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA*, 22(1), 66-71.
- [31] Kanaya, A., Deie, M., Adachi, N., Nishimori, M., Yanada, S., & Ochi, M. (2007). Intra-articular injection of mesenchymal stromal cells in partially torn anterior cruciate ligaments in a rat model. *Arthroscopy: The Journal of Arthroscopic & Related Surgery: Official Publication of the Arthroscopy Association of North America and the International Arthroscopy Association*, 23(6), 610-617.
- [32] Figueroa, D., Espinosa, M., Calvo, R., Scheu, M., Vaisman, A., Gallegos, M., & Conget, P. (2014). Anterior cruciate ligament regeneration using mesenchymal stem cells and collagen type I scaffold in a rabbit model. *Knee Surgery, Sports Traumatology, Arthroscopy: Official Journal of the ESSKA*, 22(5), 1196-1202.

- [33] Vannini, F., Cavallo, M., Ramponi, L., Castagnini, F., Massimi, S., Giannini, S., & Buda, R. E. (2017). Return to sports after bone marrow-derived cell transplantation for osteochondral lesions of the talus. *Cartilage*, 8(1), 80-87.
- [34] Sheyn, D., Kallai, I., Tawackoli, W., et al. (2011). Gene-modified adult stem cells regenerate vertebral bone defect in a rat model. *Mol Pharm*; 8: 1592-1601.
- [35] Centeno, C.J., Busse, D., Kisiday, J., et al. (2008). Increased knee cartilage volume in degenerative joint disease using percutaneously implanted, autologous mesenchymal stem cells. *Pain Physician*; 11: 343-53
- [36] Ota, S., Uehara, K., Nozaki, M., et al. (2011). Intramuscular transplantation of muscle-derived stem cells accelerates skeletal muscle healing after contusion injury via enhancement of angiogenesis. *Am J Sports Med*; 39: 1912-1922.
- [37] Horie, M., Sekiya, I., Muneta, T., et al. (2009). Intra-articular injected stem cells differentiate into meniscal cells directly and promote meniscal regeneration without mobilisation to distant organs in rat massive meniscal defect. *Stem Cells*; 27: 878-887.
- [38] Izuta, Y., Ochi, M., Adachi, N., Deie, M., Yamasaki, T., Shinomiya, R. (2005). Meniscus repair using bone marrow-derived mesenchymal stem cells: experimental study using green fluorescent protein transgenic rats. *Knee*; 12: 217-223.
- [39] Dave, L. Y., Nyland, J., McKee, P. B., & Caborn, D. N. (2012). Mesenchymal stem cell therapy in the sports knee: where are we in 2011? *Sports health*, 4(3), 252-257.



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