



## THE POTENTIALITY OF MESENCHYMAL STEM CELLS IN THE REHABILITATION OF EQUINE TENDONITIS

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### ABSTRACT

Stem cell now plays an important role as replacement treatment for many chronic diseases or damaged tissues. It develops to be promising key to cure or reduction of many incurable cases. Many scientists revealed that the stem cell represented as a current issues and future directions towered specific treatment for intractable diseases. Tendon injuries and inflammation (tendonitis) represented the frequency cause of early retirement or depletion among racing horses. Consequently the morbidity rate of these diseases is increased because the healing of the tendon is functionally insufficient. However, a plurality of therapies are conducted of tendonitis in horses, but there is a few conformation for the further information of the succeeded of curative. The aim of this comprehensive review out lights the role of Mesenchymal stromal cell (MSCs) for the treatment of tendon injuries and/or tendonitis in horses. The use of MSCs for injured or inflamed tendon has become considerable interest by veterinary domain because it is a simple transformation of developing the biotechnology for applying in the clinical condition. In the same way, more applied research has focused on horses. Therefore, MSCs is considered as favorable treatment assistance in allogeneic cell inoculation, since they exhibit minimal degree of immune reaction or immunogenicity and immune modification service.

**Keywords:** stem cells, msenchymal stem cells, mesenchymal stromal sells, tendonitis, stem cell therapy, equine.

### Introduction

Stem cell therapy provides prospective solutions for a diversity of severe acute/chronic diseases for which actual medical and/or surgical acceptances predominantly do not promote genuinely efficient therapies. This has led to proficiently transferable from theoretical or empirical studies to clinical applications (Stewart and Stewart 2011; Barrachina et al., 2018; Gugjoo and Sharma 2019). Researchers have lately taken into account studies on MSCs since these cells are considered an excellent therapeutic source for treatment clinicians, in both human and veterinary medicine. Consequently, the utilizing of MSCs in orthopaedic treatment (treatment of injured bone) has currently gained a highly significant role (Renzi et al., 2013; Durgam and Stewart 2017; Gugjoo and Sharma 2019; Shojaee and Parham 2019; Gugjoo et al., 2020; Javanshir et al., 2020).

MSCs is of special importance both for substantial study and for the curative programme of musculoskeletal disease in the equine, particularly in horses. In the last decade, mesenchymal stromal cells (MSCs) have achieved great attentiveness in equine therapy (Renzi et al., 2013; Durgam and Stewart 2017; Gugjoo and Sharma 2019; Shojaee and Parham 2019; Gugjoo et al., 2020; Javanshir et al., 2020). The first utilization of equine stem cell has been reviewed by Smith (2003) and then followed by a number of studies such as Richardson et al., (2007) and Godwin et al., (2012). Moreover, Del et al. (2008) pointed out those MSCs are speculated as a favourable treatment for assistance in cell inoculation, since they exhibit a minimal degree of immune reaction, immune inhibition and genetic mutation. Even though, MSCs are considered as a highly acknowledged method for the remediation of equine musculoskeletal diseases (Taylor et al., 2007), there is little evidence to support information about long-term medication with the clinical information, as abundant empirical clinical investigations are complicated in the multiform therapeutic programme (Schnable et al., 2013).

The main purpose of this review is to evaluate the effectiveness of stem cell local implantation in equine tendon rehabilitation. Particularly, this review will focus on the most important applications of stem cell in veterinary equine medicine. In addition, this review will investigate the role of animal models as they become widely utilized to discuss the features and possibilities of MSCs for prospective of this new biotechnology to apply in human therapy. Also, it will highlight on the future spectacle of MSCs in the treatment of equine tendonitis.

## **2.1. Data analysis and Discussion**

### **2.1.1. Stem cells: an overview**

The features of the stem cells or Mesenchymal Stromal Cells (MSCs) are spindle formative, malleable and adhesive cells, which are extracted by special technique from bone marrow, fatty tissue and other tissue provenance (Gugjoo and Sharma 2019), and they have the capability for growing and differentiation to another type of tissue in laboratory experiments (Romero et al., 2017). There are pressures and challenges in cases of embryonic stem cells because these types of cells are isolated from the umbilical cord of the fetus. Therefore, instead of these cells, scientists have used MSCs since they are commonly widely accepted by the community. Moreover, these cells are present in certain tissues of the body as mentioned before and they have minimal carcinogenic material than other types of fetal origin (Koh et al., 2015). However, in contemporary times fetal and mature stem cell has expanded into different disciplines because of a multitude of studies which have become more interesting to many scientists. Therefore, their application enters into biotechnology and regenerative therapy. As a result, several tissues, for instance bone marrow the umbilical cord and fatty tissue have been determined as a source of equine MSCs by many researchers which have been utilized in vitro (Vidal et al., 2012).

The outstanding progression of MSCs and their correlation with the biotechnological medications obligations has been applied together by medicinal and veterinary clinicians (Barrachina et al., 2018), in following cases: irreparable injuries; inflammation discovering during rehabilitation; or the presence of necrotic lesions in damaged tissue which prevents efficient medication. Consequently, many scientists in veterinary discipline have been continuing to use MSCs at the beginning of these treatments, essentially concerning the orthopaedic implementations of equine therapy (Alves et al., 2011; De Schauwer et al., 2013; Durgam and Stewart 2017; Gugjoo and Sharma 2019; Shojaei and Parham 2019; Gugjoo et al., 2020; Javanshir et al., 2020).

### **2.1.2. Development of stem cells for therapeutic purpose**

The most characteristic aspect of stem cell, it has been originated from different tissue with multifunction activity by which it has the ability to share in regenerative treatment of tendon, ligament, muscle, cartilage and bone (Del et al. 2008). Another point is that the comparative consideration for usage of stem cells in clinical application has encouraged a lot of studies to start proceeding for the utility of MSCs for tendon and skeletal muscle reformation in animals (Del Bue et al., 2008; Singh et al., 2015; Ardakani and Khan 2016; Gugjoo et al., 2018; Gugjoo et al., 2020). In the same vein, Dev et al. (2012) showed that the specific large animal samples are similar to human morphophysiology. This may provide a model which can imitate the human anatomy and physiology for therapeutic purposes. Therefore, the stem cell can be considered as a basic line to enhance therapies for humans whereas many infections and wounds of tendon and ligament are common incidence in animals as well as in human (Yadav et al., 2012).

Smith, (2003) has shown that the affection of the tendon has had a high significant morbidity in both humans and animals especially horses. The inability of walking will take more than four months for healing and the horse will not return to the normal performance. This is because the tendon has taken a longer time for healing but the formative cicatrix in this rehabilitation is insufficiently showing compared to the natural tendon (Carvalho et al., 2014). Consequently, MSCs has been introduced in various surgical techniques to repair tendonitis in horses and have been established as an appropriate treatment in equine therapy (Lacitignda, 2008; Carvalho et al., 2014). Somewhat similarly, Schnabel et al., (2013) stated that the major source of stem cell in equine therapy is from the fatty tissue and bone marrow derived MSCs. In addition, they elucidate that

MSCs are utilized after proliferation and implanted in injured tendon. Therefore, Cipriani et al. (2013) have explained the responsibility of stem cell on the conservation of mature mesenchymal tissues and turning of natural regeneration cells. They have shown that all stem cells are perivascular cells which interfere with blood cells in a complicated composition in certain areas and this permits them to indicate and detect an incident which is occurring in the animal body, be it damage or infection. On the other hand, Stewart and Stewart (2011) stated in their study, there is a common idea that MSCs influence wound recovery when used for the treatment of acute inflamed tissue, but presently, there is a little evidence on the role of MSCs in the delayed recovery of injured tissue. What is more, Smith et al. (2003) have previously demonstrated that giving a high dose of stem cells in the affected area of the tendon and at the same time presenting other kinds of cell can prevent the recovery of the tendon. Eventually, this may also lead to damage to the texture of surviving tendon. Furthermore, this point has been also supported by Licitignola et al. (2008) who explained that the stem cells accomplished perfect renewal of influenced tendon in both empirical and natural wounds. Despite achievements, this biotechnology has a few disadvantages, for instance waste time, expensive prices and difficulties in the control of cell implantation in an experimental laboratory. He also suggested that the increased period of proliferation of these cells could have a severe effect on the abilities of differentiation. However, Maguire et al. (2013) explained that in recent years they have discovered a new method to make a synergistic effect between two kinds of stem cells which release unique molecules acting on the target tissue, which enhances healing tissue damage. It is clear from the previous studies when compared with most current research that stem cell has high progression in medical therapy; in spite of this, it has some disadvantages therapy (Alves et al., 2011; De Schauwer et al., 2013; Durgam and Stewart 2017; Gugjoo and Sharma 2019; Shojaee and Parham 2019; Gugjoo et al., 2020; Javanshir et al., 2020).

## **2.2. Isolation and Proliferation of Stem Cells**

Equine MSCs have been isolated in vitro from several tissues as follows: fatty tissue (De Mattos Carvalho et al., 2009; Alipour et al., 2015; Cabezas et al., 2018), fetal cord (Koch et al., 2007), bone marrow (Arnhold et al., 2007, Branly et al., 2017; Zahedi et al., 2018; Al Naem et al., 2020) and from epidermal tissue in equine hoof (Esteves et al., 2017; Al-Agele 2018; Al-agele et al., 2019). Stem cells are generally extracted by adherence technique: MSCs is positioned in culturing tissue and preserved for 1-5 days at 37 C, later the adherence cells are removed (Pacini et al., 2007). Furthermore, Richardson et al. (2009) illustrated the extraction of stem cell from the sternum after that transferring it to the lab for the proliferation of MSCs for 3 weeks and returning it back to the clinicians. Finally, injection into the injured tendon for the same case (Figure 1). This technique has become accepted in clinical applications (Carvalho et al., 2014) in the UK, Australia and Europe because more than 400 cases have been successfully managed without side effects (Lui, 2020).



**Figure 1:** Schematic illustrates the extraction of stem cell from the sternum, proliferation and returning it back to the site of injured tendon.

### **2.3. Future Perspectives of MSCs in Treatment of Injuries and Tendonitis of Horses**

In previous studies Lacitignola et al. (2008) have shown that the use of stem cells derived from bone marrow to treat injured tendon in horses has achieved great results ranging from a higher one 84%, while lower one 15% were moderate in healing. This result has been supported by the finding of Del et al. (2008) they found in their study of 16 horses had inflamed tendon when they have been treated by using MSCs which were isolated from adipose tissue and injected in different area of the affected tendon. Consequently, the result of this study has demonstrated that 14 of them were completely treated and returned to their normal performance after 8 weeks. In addition, through the period of healing no horses had difficult situation, excluding a local swelling, while the remainder two horses had not satisfy perfect healing because they have noticed that these last two horses had been affected by sub chronic inflammation in their legs. Therefore, they did not respond to treatment of MSCs. Furthermore, it has been suggested by other researchers such as Arthur et al. (2009) that stem cell incorporation with special technique is used for supporting and increasing renewal of living tissue. As a result, this method is high benefit in contrast with the traditional therapy choice reviewed by Richardson et al.(2007) and Del et al. (2008). However, Schnable et al. (2013) showed that all of the previous publishers on utilization of stem cell for the recovery of injured tendon have depended on one single dose of MSCs. In contrast they found in clinical applications, it is possible to use multiple injections depend on the recovery of inflamed tendon. In addition, Reed and Johnson (2013) noticed that the utilizing of a chemical substance represented as a delivering factor can be enhanced stem cell for the treatment of tendon injuries. Recently, Lui (2020) have stated that the recent method on the promotion of healing tendon via EVs-derived from MSCs (MSC-EVs enables and provides a new therapeutical strategy to avoid this devastating soft tissue condition. In other words, it is conspicuous from the current studies on stem cells that development of this issue of new biotechnology has taken an agreement of treatment damaged tendon, particularly in the last few years which has become more extensive with new idea to transfer it for future therapy.

#### **In conclusion**

The acknowledgement of the new biotechnology and the clinical possibility use of stem cells are dramatically enhanced in the last decade. These included different surgical empirical techniques have been introduced into the rehabilitation of inflamed tendons in horses and have been established as an appropriate treatment in equine medicine. This review supports the use of stem cells in the treatment of injured and inflamed tendon and has offered development in technical approach of stem cells. The issue of new technological method is represented as a new direction in the expansion of treatments. This current issue has distinguished between conventional treatments where it is restricted on sedative drugs and the futurity of biotechnological procedure



of stem cell. In debating proceed in equine tendonitis, it was resulted in stem cell development are displayed high prospective capacity as therapeutic factors in advanced medicine due to regenerative possibility, immune inhibition, and restrictive immunity having a high proportion of propagation in culture. Furthermore, a development of veterinary medicine represents an important role in this recent and developing technology, which has largely focused many scientists on using stem cell in animals as a sample of preclinical experimentation of human medicine. The review has centred on stem cell development for the treatment of equine tendonitis. In the future, it should better recommend to clarify further studies of the bio-physiology of stem cell to demonstrate the technicality of effective treatment.

#### **Conflict of interest**

The authors declare that they have no conflict of interest.

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