



Original Research

Mesenchymal Stem Cells Derived From Subcutaneous Fat and Platelet-Rich Plasma Used in Athletic Horses With Lameness of the Superficial Digital Flexor Tendon



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ABSTRACT

Tendinitis of superficial digital flexor tendon (SDFT) represents a major cause of injury in the equine athlete. Although numerous treatments have been described, few are effective and a great potential remains for recurrence and, in certain cases, an abrupt end to the horse's athletic career. Recently, several experiments have focused on the therapeutic potential of mesenchymal stem cells (MSCs) in cases of tendon lesions. The aim of this study was to evaluate the possible clinical application of equine adipose tissue-derived MSCs (AD-MSCs) and autologous platelet-rich plasma (PRP) for the treatment of acute injuries of tendons in sport horses. Nine athlete horses with an injury of the SDFT were enrolled. Subcutaneous fat from each horse was collected, and AD-MSCs were isolated, characterized, and injected with autologous PRP in tendon injury. The evolution of tendinopathy healing was assessed by ultrasound. Horses underwent to a 6-month rehabilitation program. The ultrasound findings have shown indicative signs of a reparative process that led to the formation of tissue morphologically comparable with healthy tissue. Recurrences observed in only two of the nine horses treated occurred for reasons not related to treatment. In fact, in horse, the lesion occurred in the same tendon but at a different point from the first; another recurrence was caused by failure to comply with the rehabilitation protocol. Our study showed that therapy with AD-MSCs and PRP for treatment of tendon injuries in the athlete horse seems to be promising. However, the post-operative treatment of the patient is an essential support for the proper remodeling of the tendon.

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1. Introduction

Mesenchymal stem cells (MSCs) are nonhematopoietic (NH) multipotent stem cells of particular interest for basic research and increasingly used as therapeutical aid for the

orthopedic injuries in the horse. Mechanical stresses cause tendon lesions of different degree (partial tears) in equine athletes. In horse, the most frequently area affected is the superficial digital flexor tendon (SDFT) [1–3]. Tendinopathy is most common in racehorses and event horses but can occur in horses used for any discipline. Tendinitis is an important cause of lameness and diminished performance in equine athletes because of its high incidence, prolonged recovery period, and high rate of recurrence. Possible

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explanations for the slow healing of tendons and, in most cases, the resulting formation of mechanically inferior extracellular matrix are probably because of the fact that tendon is a minimally vascularized tissue, presents cells that exhibit diminished mitotic activity, and the presence of few progenitor cells in the tissue.

Recurrences are related to the nonregeneration of tendon tissue and the production of a matrix of collagen fibrils that are smaller in diameter and of inferior quality, showing a reduced number of cross-links. Knowledge concerning tendon repair and its implications for the athletic capacity of the individual horses affected by tendinitis has stimulated research regarding new therapies applied to this tissue. Cell therapy using MSCs has shown promising results in several published works [4–6]. The isolation of MSCs has been described in several species and from different tissues [7,8]. Particularly, in horse, MSCs have also been isolated and differentiated from sources as umbilical cord blood, amniotic fluid, bone marrow, and adipose tissue [9–11]. Mesenchymal stem cells derived from bone marrow (BM-MSCs) and adipose tissue-derived MSCs (AD-MSCs) are the most highly characterized and are considered comparable [12]. Both have demonstrated broad multipotency with differentiation into different cell lineages, including adipocytic, osteocytic, and chondrocytic lineages [13,14]. However, the easy and repeatable access to adipose tissue, the simple isolation procedure, and the greater numbers of fresh MSCs derived from equivalent amounts of fat versus bone marrow provide a clear advantage in using AD-MSCs over BM-MSCs [11,15,16]. Adipose tissue-derived MSCs can be isolated, expanded *in vitro*, and then inoculated into the damage tissue [10] showing their utility for the treatment of musculoskeletal and osteoarticular diseases in several animal species [7,17,18]. Because these cells are readily accessible in large quantity in the horse, they have received increasing attention for the possible application for the treatment of tendon and ligament diseases. In particular, the use of AD-MSCs and their migration was evaluated after tendinitis therapy in equine [11,19].

Recently, platelet-rich plasma (PRP), an autologous concentrate of blood platelets, has been introduced as possible new therapy for the treatment of tendon injuries because it seems to represent a temporary therapy that provides important biological effects such as the increase in production of type I collagen, the proliferation of tenocytes, neovascularization, the increase of resistance, and the organization and alignment of the fibers [20–22]. In fact, the

field of AD-MSC and PRP therapies in regenerative medicine is a rapidly growing area of research, and stem cell therapy is being used for tendon regeneration, given the frequency of tendon injuries worldwide together with the technical difficulty often encountered when repairing or augmenting tendons. Considering that tendons connect bone to muscle and are essential for transmitting forces to produce joint movement, tendon injury is a major cause of population morbidity.

Based on that the aim of this study was to evaluate the production of equine AD-MSCs and PRP autologous and the possible clinical application of cellular therapy for the treatment of acute injuries of tendons in horse. Particularly, to assess whether cellular therapy can replace drug therapy, the clinical effect of a single intratendinous injection of AD-MSCs and autologous PRP was evaluated in athletic horses with spontaneous and acute lameness of the SDFT.

2. Materials and Methods

2.1. Animals

Nine athletic horses (three males, three females, and three geldings), ranging in age from 3 to 12 years and with mean body weight of 450 ± 60 kg, were recruited based on the presence of lesion in SDFT in the forelimb (Table 1). To be eligible, the horses had to be cared for by attentive owners who agreed by informed consent to participate in this clinical study, to follow a set schedule of veterinary appointments and to observe their horses for the entire study period. Before enrollment, all horses underwent routine clinical chemistry and hematologic evaluation to ensure overall health. The clinical examination revealed the presence of pain, edema, and swelling of the affected metacarpal region. Tendinitis was evaluated by ultrasound examinations using MicroMaxx portable ultrasound system with 7.5-MHz linear probe provided with gel pad; the Sony printer provided the ultrasound images. Lesion sites were identified according to the Davis and Smith [23] model. The degrees of echogenicity (transverse section) and fiber alignment (longitudinal section) of each lesion were recorded to assess the severity of tendon injuries (Reef [24]). All horses were treated with regenerative therapies as AD-MSCs and PRP, defined as the alternative therapy useful to reduce the degeneration of tendinitis.

Table 1
Summary of clinical cases treated.

Horses	Age	Gender	Breed	Attitude	Lesion	Lameness	Relapse
1	4	Female	Sella Italiana	Jumping	Recurrence, right, SDFT	Yes	No
2	15	Gelding	Sconosciuta	Jumping	Primary, left, SDFT	Yes	No
3	5	Female	Quarter Horse	Barrel racing	Primary, left, SDFT	No	No
4	12	Gelding	Holsteiner	Jumping	Primary, right, SDFT	Yes	Yes
5	8	Male	Quarter Horse	Barrel racing	Recurrence, right, SDFT	Yes	No
6	8	Male	Quarter Horse	Barrel racing	Primary, left, SDFT	Yes	Yes
7	3	Male	Quarter Horse	Raining	Primary, left, SDFT	No	No
8	5	Gelding	Sella Italiana	Jumping	Primary, left, SDFT	No	No
9	7	Female	Sella Italiana	Jumping	Recurrence, left, SDFT	Yes	No

Abbreviation: SDFT, superficial digital flexor tendon in the forelimb.

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