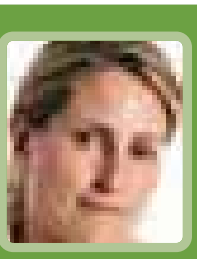
Equine tendon injury: old treatments fired and stem cells promoted?



Dr CHARLOTTE AVELLA and Professor ROGER SMITH discuss equine tendon injury repair in the 21st century

Introduction

Tendon injury is significant in horses due to its common occurrence, the lack of a highly effective treatment, the requirement for lengthy rehabilitation, and the risk of re-injury.

In horses, the superficial digital flexor tendon (SDFT) of the forelimb is the most commonly injured tendon.

Tendinopathy is most common in racehorses and event horses but can occur in horses used for any discipline. A recent study of 148 National Hunt racehorses in training, at 10 training yards in the UK, revealed a 24% prevalence of SDFT tendinopathy detected using ultrasonography (Avella *et al.*, 2009).

Diagnosis of tendon injury

Diagnosis of strain-induced tendon injury is usually based on history (frequently a preceding period of exercise) and the development of the signs of inflammation (pain, heat, swelling, and lameness) over the affected structure. Once the inflammatory phase has passed (within 1 or 2 weeks), lameness usually resolves rapidly.

Most acute cases of SDFT tendinopathy present ultrasonographically with a reduction in echogenicity resulting in a hypoechoic or anechoic appearance to the lesion. This typically central area or "core lesion", which is usually a well demarcated hypoechoic or anechoic region, represents a loss of normal tendon architecture and the accumulation of fluid. Tendon cross-sectional area is usually increased and the longitudinal fibre pattern disrupted.

Charlotte Avella, BVSc, PhD, CertEP, CertES(Orth), MRCVS, graduated from Bristol in 2000 and is currently working as a staff clinician in equine diagnostic imaging at the RVC's Equine Referral Hospital.
Roger K. W. Smith, MA, VetMB, DipECVS, PhD, DEO, MRCVS, qualified from Cambridge in 1987. In 2003 he was appointed professor in equine surgery at the RVC. His major research interest is understanding the aetiology of tendinopathy in conjunction with research into regenerative therapies.

Pathophysiology of tendon injury and repair

Once the peak load on the tendon overcomes its structural strength, there is physical disruption to the tendon matrix. The clinical injury varies in degree from fibrillar slippage, with breakage of crosslinking elements, to fibrillar rupture and, in some cases, complete separation of tendon tissue.

Once this occurs, the damage created induces a repair process that results in inflammation followed by fibroplasia. Thus, synthesis of scar tissue occurs that has a composition which is different from that of tendon, with a higher ratio of type III:I collagen (about 50% compared with 10% for normal tendon), a higher hydration, and higher levels of glycosaminoglycans (GAGs) (Birch *et al.*, 1998).

Although mature scar tissue tends to be less stiff as a material than tendon, because large amounts are formed, the scarred tendon often results in a stiffer tendon than the original. As a result, the healed tendon becomes strong but it is functionally inferior to normal tendon, predisposing it to re-injury, often at sites adjacent to the original injury.

Treatment of tendon injury

In 1964, Asheim described the common treatment of tendon and ligament injuries as "phlebotomy, local cooling, plaster bandaging and rest".

Over the last four decades, many treatments have been proposed for the management of tendon injury, although few, if any, have convincing supporting evidence of efficacy, and some can even be considered deleterious or detrimental to healing. However, the basic principles described by Asheim of cooling, support, and rest remain integral parts of the management protocol.

New advances: stem cell therapy

The hypothesis for stem cell therapy for the treatment of tendon injuries is that implanted bone marrow-derived mesenchymal stromal cells (MSCs) will be capable of synthesising matrix more like tendon and less like scar tissue to provide a superior functional outcome.

Figure 1. Tendon injuries are most common in racehorses and eventers.

An initial safety trial was executed to provide proof of concept. Six horses that had moderate to severe SDFT injuries were recruited onto the trial which demonstrated that the MSCs therapy did not have adverse effects such as formation of inappropriate tissue.

The use of MSCs for intralesional treatment of tendinopathy offers the prospect of tissue regeneration rather than repair. MSCs have the potential to differentiate into tenocytes and to regenerate tendon matrix, thereby creating a repair that is functionally superior to fibrous scar tissue.

Initial studies have included the isolation of MSCs from either bone marrow or fat, followed by either direct implantation or expansion in vitro before implantation (Dahlgren *et al.*, 2002).

Technique

Bone marrow (BM) is recovered from the sternum following the diagnosis and assessment of tendon injury. Using standing sedation and local anaesthesia, the inter-sternal space identified using ultrasonography and the BM from the sternebrae either side is aspirated using a Jamshidi needle. The BM derived cells are cultured *in vitro* and the nucleated adherent cell population is recovered and re-suspended in citrated BM supernatant.

Implantation is performed at approximately 2-3 weeks after BM aspiration. The horse is sedated and local regional analgesia of the palmar metacarpal soft tissues is performed. The MSCs are injected at specific sites along the tendon depending on the extent of the injury. The implantation of the MSCs is performed using ultrasound guidance.

Ultrasonographic assessment of outcome

Horses with tendon injuries treated with stem-cell therapy have demonstrated rapid ultrasonographic improvement of lesions. This includes increased echogenicity in the initially hypoechoic lesion reaching similar echogenicity to normal tendon over several months.

In addition to improved density of the fibre pattern, evidence of lengthening of the linearly arranged fibres was apparent. The sequential ultrasound examinations have provided evidence of good to satisfactory healing following stem cell therapy.

Functional outcome

The long-term outcome of stem cell therapy is assessed by clinical

Figure 2. Ultrasonography image showing a core lesion within the superficial digital flexor tendon.

Figure 3. Professor Roger Smith performing an ultrasound examination at the Royal Veterinary College Equine Referral Hospital.

examination, the presence of ultrasonographic evidence of tendon repair and ultimately by whether the horse re-injures. Prevention of re-injury is the primary aim of tendon therapy.

To date, over 1,500 horses with SDFT tendinopathy have been treated with intralesional autologus MSCs. Analysis of the clinical outcome in 113 national hunt racehorses with two years of follow-up post-treatment gave a re-injury rate of 28.9% (Smith, 2010).

This re-injury rate is significantly better than data previously reported for a similar population of NH horses treated conventionally and analysed in the same way (56%) (Dyson *et al*., 2004).

Conventional therapy with which stem cell therapy was compared included controlled exercise alone, or controlled exercise combined with intralesional tendon treatments with hyaluronic acid or polysulphated glycosaminoglycans (PSGAGs).

Conclusion

The use of bone marrow derived autologus mesenchymal stromal cells intralesionally to treat tendon injury appears to significantly decrease the risk of re-injury, thus potentially extending the athletic career of the horse and reducing morbidity.

References

Asheim, A. (1964) Surgical treatment of tendon injuries in the horse. *J Am Vet Med Assoc* **145**: 447.

Avella, C. S., Ely, E. R., Verheyen, K. L. P., Price, J. S., Wood, J. L. N. and Smith, R. K. W. (2009) Ultrasonographic assessment of the superficial digital flexor tendons of National Hunt racehorses in training over two racing seasons. *Equine Vet J* **41** (5): 449-454.

Birch, H. L., Bailey, A. J. and Goodship, A. E. (1998) Macroscopic "degeneration" of equine superficial digital flexor tendon is accompanied by a change in extracellular matrix composition. *Equine Vet J* **30**: 534-539.

Dahlgren, L. A., van der Meulen, M. C. H. and Bertram, J. E. A. *et al* (2002) Insulin-like growth factor-I improves cellular and molecular aspects of healing in a collagenase-induced model of flexor tendinitis. *Journal of Orthopaedic Research* **20**: 910.

Dyson, S. J. (2004) Medical management of superficial digital flexor tendonitis: a comparative study in 219 horses (1992-2000). *Equine Vet J* **36**: 415-419.

Smith, R. K. W. (2010) Bone marrow-derived stem cells for tendon and ligament repair. *Proceedings of the British Equine Veterinary Association Congress*, September: pp119-120.

National Equine Forum in March

THE 2011 National Equine Forum (NEF) is to be held on 8th March 2011 at The Royal Society in London. Among the speakers will be James Paice, Minister of State for Agriculture and Food; either the president or vice-president of the FEI will be available to talk about "clean sport" and its global impact; Professor Tim Morris; and Georgina Crossman, a PhD research student at the Centre for Rural Policy Research at the University of Exeter, will cover disease surveillance and management in the EU.

Veterinary topics will include a presentation from Professor Charlotte Maltin on the maintenance of the equine gene pool, and Nick Thompson and Dr Simon Baker will discuss the question, "Homoeopathy – science or alchemy?"

Tickets are available at £100 per person. To apply, contact Tracy Allen: e-mail teallen@warkscol.ac.uk. For further information on the NEF see www.bef.co.uk.

Charities welcome recommendations of 'responsibility and cost sharing' report

A GROUP of seven animal and equine charities has welcomed recommendations from an independent advisory group that would give the industry a say in policy decision making on animal welfare and disease issues.

The charities had previously raised serious concerns over proposals for the creation of a new animal health body proposed by DEFRA under the previous government, but which have now been dropped.

They had expressed fears that the new structure would be unnecessarily cumbersome and complex.

Following the publication of the report by The England Advisory Group on Responsibility and Cost Sharing (*see front page*), the charities said they were particularly happy with the recommendation that animal health policy and animal welfare policy should not be separated.

They said they were pleased to note that the Radcliffe Report agreed with current DEFRA thinking that the earlier suggestion of a new independent animal health body should not be pursued. This is especially relevant as such a structure would have led to further fragmentation of the regulatory framework and therefore impeded existing disease control arrangements.

The charities describe some of the report's suggestions as "bold and innovative" but add they will require detailed consideration by DEFRA and stakeholders, not least on how real responsibility sharing could be achieved.

Roly Owers from World Horse Welfare said he was optimistic that DEFRA would consider the sensible recommendations in the report which would allow real responsibility sharing to be achieved with all sectors of the equine industry, including the charitable sector."

• The seven charities involved are: World Horse Welfare, The Horse Trust, the Animal Health Trust, Redwings Horse Sanctuary, Wood Green Animal Shelters, HorseWorld and The Donkey Sanctuary.