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Regenerating equine tendon using autologous mesenchymal stem cells

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Tendon injuries

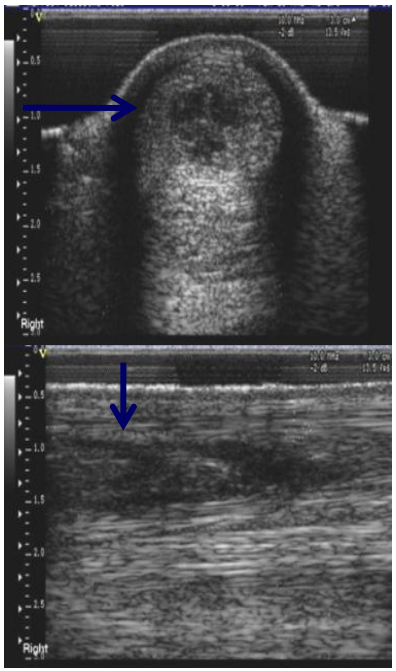
- Tendon injuries in the racehorse, especially the ‘jumper’, are very common.
- Following initial injury, re-injury rates after rest, treatment and rehabilitation are up to 66%.
- In the past, tendons have always healed with inelastic scar tissue, nowhere near as ‘elastic’ as the original tissue, hence the re-injury problem.

Treatment for tendon injuries

- Clinicians have been searching for a treatment method that would make injured tendons 'as good as new'.
- Mesenchymal stem cells are 'multipurpose' cells which can be harvested from the injured horse, and can then have profound effects on the tissue into which they are placed.
- In this study, the stem cells were derived from bone marrow collected from the injured horse.
- Would, and could, these cells increase the quality of repair if they were injected into injured tendons?

Superficial digital flexor tendon injury in racehorses

- Very common disease
  - Almost one quarter of National Hunt horses have tendon disease (Avella et al. 2009)



Why use regenerative medicine for tendon disease?

Consequences of injury

- Altered biomechanics
- Reduced performance
- High frequency of re-injury (up to 67%; Dyson, 2004)

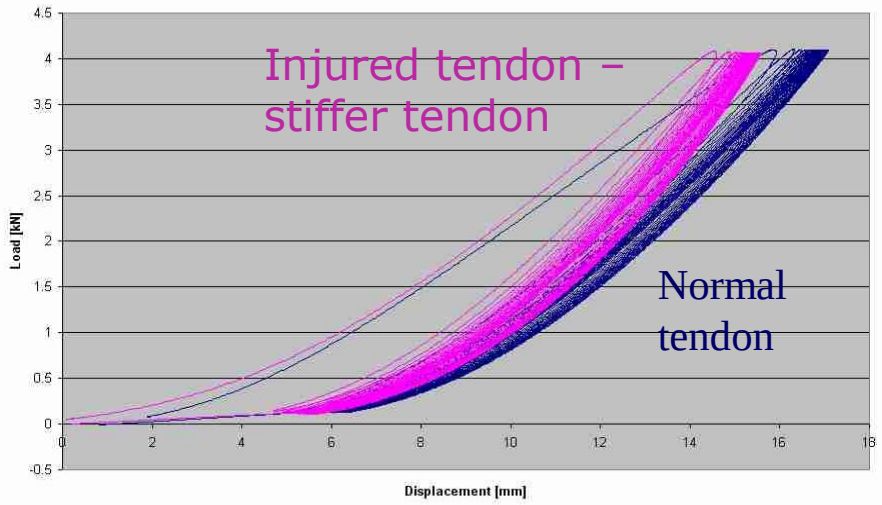
Main aim of therapy

- To optimise function

Why use regenerative medicine for tendon disease?

Implanted mesenchymal stem cells might induce a matrix more like tendon and less like scar tissue:

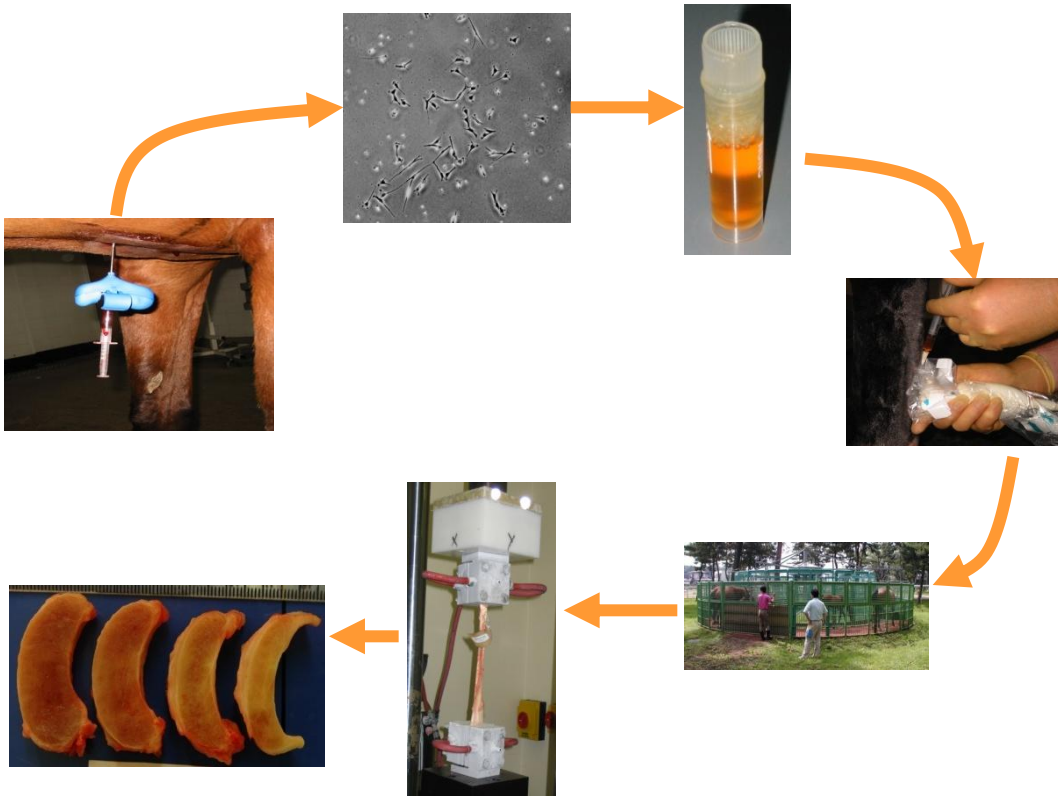
- Normalisation of biomechanical, organisational and compositional parameters
- Better functional outcome



Ex-vivo tendon mechanics

Experimental study

- Horses with naturally-occurring injury within one month of injury.
- Sequentially assigned to stem cell and saline control groups.
- Given 6 months of controlled exercise before euthanasia.
- Clinical evaluation.
- Post mortem analysis
  - Mechanical, histological and compositional analyses of tendon.

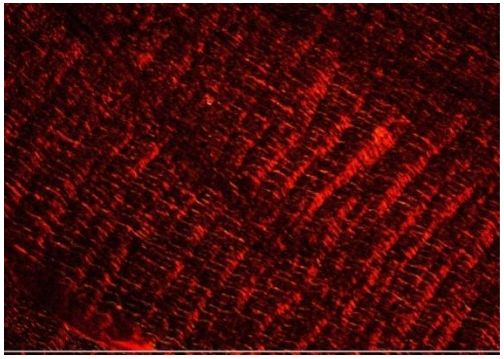


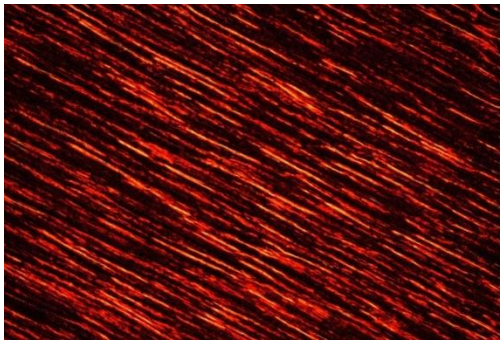
How did the stem cell treated tendons compare to the others?

Stem cell-treated tendons had parameters more similar to normal 'uninjured' tendon than after saline injection

- Reduced stiffness
- Smaller cross-sectional area
- Reduced cellularity
  - Blinded histological scoring
  - DNA content
- Improved fibrillar organisation
- Greater crimp
- Lower glycosaminoglycan content

- No difference in water or collagen content





Conclusions

- Implantation of bone marrow derived stem cells induced a 'normalisation' of the tendon matrix, although not all parameters were statistically significantly different from saline-treated controls.

- This study has provided supportive evidence for the clinical use of bone marrow derived stem cells in clinical cases of superficial digital flexor tendinopathy (Godwin et al., 2012).
  - Further supported by significantly reduced re-injury rates when compared to published series of conventionally treated cases (Dyson 2004; O'Meara et al., 2010).

Commentary on conclusions

- Only small numbers of horses were used in each group, and this makes PROVING an effect very difficult.
- This meant that some of the findings were not statistically significant - most importantly in the findings of eventual stiffness of the tendon in the treated and control groups.
- As it is a more ‘elastic’ repaired tendon we are chasing, this is disappointing.

Commentary on conclusions

- What's encouraging though is that there was a TREND in improvement of these factors, which may show as statistically significant in a larger study.

- Under the microscope, the treated tendons DID show several features indicative of an improved quality of repair. These included reduced cellularity and improved collagen fibril organisation when compared with saline injected tendons. In other words the tissue looked more like an organised 'rope' than a disorganised 'scar'.

Commentary on conclusions

- Similarly the degree of 'crimp' pattern (the degree of regular folding and re-folding of fibres which allows the tendon to stretch and rebound in loading seen in healthy tendons) was also improved in tendons treated with stem cells when compared with those treated with saline.

- What we really need now is PROOF that all of these changes make the repaired tendon good enough to bear the huge loads involved in racing, without the high risk of re-injury we have always seen in the past.

Commentary on conclusions

- In the study recently published on clinical efficacy (Godwin et al., 2012), the treatment DID show a significantly increased success rate compared to all previous treatments in National Hunt horses, but not in Flat racing horses, where the numbers treated were very small

Find more information about tendon injuries in racehorses

- Musculoskeletal disease and injury, now and in the future. Part 2. Tendon and Ligament injuries, PD Clegg:

  http://onlinelibrary.wiley.com/doi/10.1111/j.2042-3306.2012.00563.x/full

Scientist's summary

- A strained tendon remains one of the most debilitating injuries of the Thoroughbred racehorse, and is often career-ending.

- Recurrence rates of around 70% are the norm following many different types of treatment, none of which have proved to be systematically successful.

- This study sought to verify the hypothesis that implantation into the site of the tendon injury of mesenchymal stem cells, derived initially from the bone marrow in the sternum and then multiplied up in the laboratory by tissue culture, would improve the regeneration quality of repair, and ultimately the elasticity and strength of the injured tendon on recovery.

Scientist's summary

- The study was carried out on ten horses; five had saline injected into the tendon as a control procedure and the remaining five had mesenchymal stem cells injected instead into the same location.

- The horses were exercised only on a horse-walker for 6 months and were then subjected to euthanasia and the tendons harvested. They were then examined under a microscope to assess the structure of the tendon, as well as being tested for strength and stiffness by the whole tendon being removed and clamped into a testing jig where these factors could be measured.

- The small number of cases in both the treatment and control groups unfortunately impacted on the ability of the study to show some of the changes to be statistically significant.

Scientist's summary

- So what did implantation of the stem cells do?
  - The cross sectional area of treated tendons were significantly smaller after 6 months than that of the saline controls. In other words, the leg 'fined down' following stem cell treatment than in those treated with an inert placebo (saline).
  - The stiffness of the tendon did not differ between treated and control groups. An ideal treatment for tendon injury would result in a recovered tendon which was not 'stiff', as stiffness is a feature of poorly organized scar tissue, and the limiting factor for successful repair in the tendon.

Scientist's summary

- The normal tendon acts like a very strong elastic band, but this ability is significantly reduced by stiff fibrous scar tissue following injury.

- Stiffness of treated and control tendons following the 6 month period of recovery was not shown to be statistically significantly different, although there were tantalizing hints that there was a trend in this direction.

- The lack of significance of these differences may be a reflection of the low number of cases used, which makes any small difference harder to demonstrate as significant statistically above and beyond normal variation.

Scientist's summary

- Under the microscope the treated tendons did show several features indicative of an improved quality of repair and these included reduced cellularity and improved collagen fibril organization when compared with saline injected tendons, in other words the tissue looked more like an organized 'rope' than a disorganized 'scar'.

- Similarly the degree of 'crimp' pattern (the degree of regular folding and re-folding of fibres which allows the tendon to stretch and rebound in loading, seen in healthy tendons) was also improved in tendons treated with stem cells than compared with those treated with saline.

Scientist's summary

Implications and Conclusions:

- The authors verified that stem cells can be successfully collected from the sternum, multiplied in culture and re-injected into the tendon.

- They showed that the injection of the stem cells reduces the size of the affected tendon at 6 months of age and that under the microscope there are several features indicating an improved quality of repair.

Scientist's summary

- However, the stiffness of the tendon itself was not significantly affected by the treatment.

- Although there are several pointers in the direction of improved repair, this still has to be vindicated by showing that the repaired tendon is able to act as the normal, super strong elastic band required, particularly by the horse racing on the flat, to compete successfully again following tendon injury.