

A review of the equine suspensory ligament: Injury prone yet understudied

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Abstract

The suspensory ligament (SL) is a key component of the elaborate and highly adapted suspensory apparatus in the horse. In addition to contributing to stabilisation of the metacarpophalangeal joint, the SL has a spring like function to reduce the energetic cost of locomotion. Although the SL is highly prone to injury in horses of all ages and competing in a wide range of disciplines, knowledge regarding fundamental structure–function relationships in the SL is lacking, particularly compared with other injury-prone tendinous structures such as the superficial digital flexor tendon. In this review, we discuss current knowledge of SL composition, structure and mechanical properties and describe the epidemiology, aetiology and pathophysiology of injuries. We evaluate different diagnostic approaches and treatment modalities and identify key areas for future research.

KEYWORDS

equine, function, injury, structure, Suspensory ligament

1 | SUSPENSORY LIGAMENT COMPOSITION AND STRUCTURE

The specialised function of the suspensory ligament (SL) is achieved by the highly adapted composition and structural arrangement of the tissue comprising the ligament. The SL originates on the proximo-palmar/plantar aspect of the third metacarpus/tarsus and continues distally, bifurcating and inserting onto the abaxial surface of the proximal sesamoid bones (Figure 1). The extensor branches extend medially and laterally around the metacarpophalangeal joint, fusing with the common digital extensor tendon.^{3,4} The SL is often divided into three regions, the proximal portion, the body, and the branches (Figure 1B,C). The SL is the anatomical equivalent of the interosseus muscle in other species, and may be referred to by that name in the horse. However, the equine SL has become highly adapted during evolution, with an almost complete loss of muscle fibres except in the proximal region, and an increase in collagen content.⁴ These evolutionary adaptations have resulted in the development of a unique structure, with characteristics reminiscent of tendon, ligament and muscle.⁵

The SL has several functions during locomotion. It is a key component of suspensory apparatus, preventing hyperextension of the metacarpophalangeal joint during stance phase.^{3,4} Indeed, at maximal metacarpophalangeal joint extension the SL and accessory ligaments of the superficial and deep digital flexor tendons are predicted to contribute over half of the total support moment around the joint.⁶ The SL also functions to store and return elastic energy in a similar manner to the forelimb superficial digital flexor tendon (SDFT), reducing the energetic cost of locomotion.⁷ At rest, the SL contributes to the passive stay apparatus, allowing horses to remain standing for long periods of time with little muscular effort.^{8,9}

The predominant extracellular matrix (ECM) protein that comprises the SL is type I collagen, with values varying from 34% to 65% dry weight (Table 1).^{5,11} The collagen content varies along the length of the ligament, with a greater collagen content distally, as the proportion of muscular tissue diminishes.⁵ These values are lower than those in the SDFT which is ~75% collagen by dry weight (Table 1). Collagen molecules are stabilised by intermolecular crosslinks, including hydroxylysyl pyridinoline (HP) and lysyl pyridinoline (LP). While HP concentrations are significantly lower in

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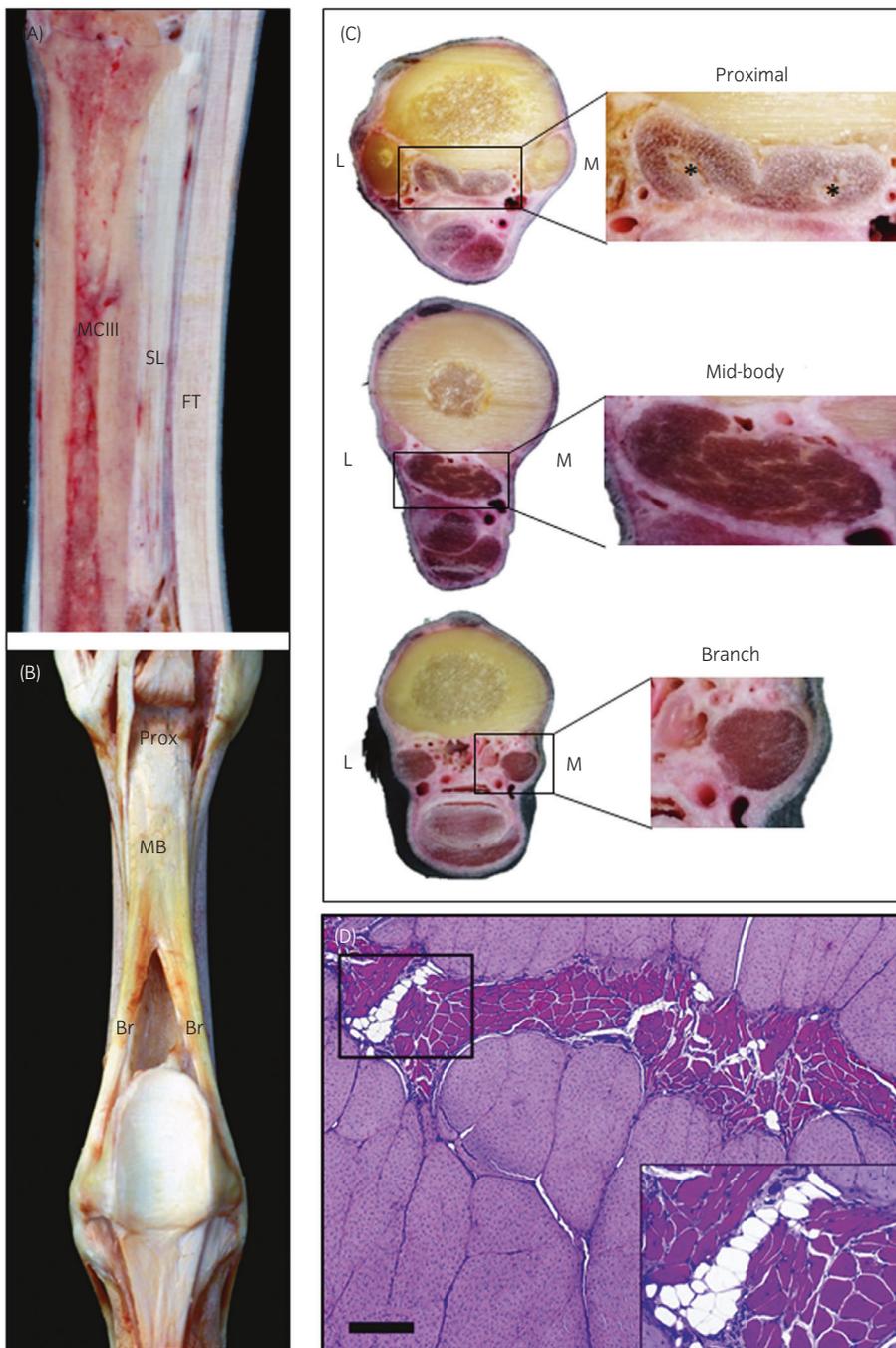


FIGURE 1 The location, macroscopic and histological appearance of the suspensory ligament. Sagittal section through the forelimb showing the location of the suspensory ligament (SL), third metacarpal bone (MCIII) and flexor tendons (FT) (A). Palmar view showing proximal (Prox), mid-body (MB) and branch (Br) regions of the suspensory ligament (B). Transverse sections through the forelimb showing the appearance of the proximal, mid-body and branches of the suspensory ligament. Interfascicular spaces are denoted by * (C). Histological section from the mid-body showing the presence of muscle fibres within the interfascicular spaces present along the length of the ligament. Scale bar: 200 μm (D). Adapted from Denoix,¹ Schramme et al.² and Royal Veterinary College Equine Distal Limb Resource (www.rvc.ac.uk/static/review/equine-distal-limb/index.html) with permission from the publishers.

the SL compared with the SDFT, the concentrations of other crosslinks are similar and do not change along the length of the SL, suggesting a broadly similar crosslink profile between the two tissues.^{5,12} Another crosslink, pentosidine, accumulates spontaneously with ageing and therefore can be used as a marker of tissue turnover.^{13,14} Higher pentosidine levels have been reported in the proximal region of the SL compared with the mid-body and branches, indicating lower turnover of collagen proximally, which may contribute to the increased risk of injury to this region.⁵ Pentosidine levels in the mid-metacarpal region are higher in the SL than in the SDFT, indicating that the SL is turned over more slowly (Table 1).

As in other tendons and ligaments, the collagen in the SL is highly aligned and arranged in a hierarchical manner, with type I collagen

fibrils grouped into fascicles, which are surrounded by interfascicular matrix (also referred to as endotenon).⁵ The diameter of the collagen fibrils follows a bimodal distribution, similar to that in the SDFT.¹⁵ The mass average fibril diameter, however, is significantly lower in the SL ($122 \pm 14 \text{ nm}$, $n = 6$) than in the SDFT ($169 \pm 19 \text{ nm}$, $n = 6$) (Figure 2), although both structures have a higher proportion of small diameter fibrils than the DDFT and CDET. This likely reflects the similar function of the SDFT and SL, as it has been shown that a lower mass average fibril diameter is associated with a lower elastic modulus.¹²

The noncollagenous protein content of the SL is not well established; however, it has been shown that glycosaminoglycan (GAG) content, a measure of proteoglycan levels, varies along the SL length,

TABLE 1 Comparison of SDFT and SL composition in the mid-metacarpal region, measured using standard biochemical techniques in our laboratory.

| | Superficial digital flexor tendon | Suspensory ligament |
|-----------------------------|-----------------------------------|---------------------|
| Water (%) | 64.91 ± 1.64 | 67.76 ± 1.30*** |
| Collagen (%) | 75.81 ± 8.20 | 65.11 ± 9.16** |
| GAG (µg/mg) | 10.40 ± 4.86 | 13.30 ± 5.32* |
| DNA (µg/mg) | 0.54 ± 0.11 | 0.69 ± 0.17*** |
| Pentosidine (mM/M collagen) | 13.83 ± 9.56 | 17.33 ± 11.65*** |
| HP (mM/M collagen) | 737.84 ± 255.58 | 598.67 ± 231.82* |
| LP (mM/M collagen) | 101.51 ± 108.10 | 100.23 ± 96.90 |

Note: For further details of methodology see Thorpe.¹⁰ Significant differences between tissue types are indicated by *: **p* < 0.05; ***p* < 0.01; ****p* < 0.001. Data are shown as mean ± SD. *N* = 32.

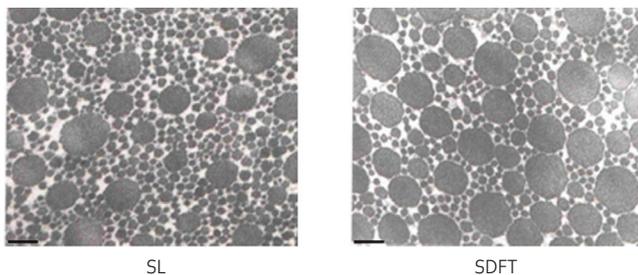


FIGURE 2 Electron micrographs showing fibril diameters in the SL and SDFT. Scale bar represents 200 nm. For further details of methodology see Smith.¹⁶

with the lowest content in the proximal region which increases distally.⁵ The SL also has a higher total sulfated GAG content compared with the SDFT (Table 1). Proteoglycans regulate collagen fibrillogenesis,¹⁷ but the abundance, location and function of specific noncollagenous proteins within the SL remains to be determined. Indeed, while advanced techniques are now available to provide a proteomic profile of ECM-rich tissues,¹⁸ these experiments are yet to be performed for the SL, meaning that our knowledge of proteins that may have an important role in tissue function are yet to be identified.

Unlike other ligamentous structures, the SL contains a high proportion of muscle fibres and other noncollagenous tissue, which varies not only along the length of the ligament but also between fore and hindlimb tendons and in different breeds. The muscle fibres are contained within two interfascicular spaces, one medially and one laterally (Figure 1C, indicated by * in inset). These spaces are evident throughout the majority of the fore and hindlimb SL, and are present slightly distal from the origin, terminating in the middle portion of the ligament branches. They are filled with variable proportions of skeletal muscle fibres, loose connective tissue, adipose tissue as well as blood vessels and nerves.² The sizes of the interfascicular spaces are also heterogeneous, increasing in the mid-portion and occupying up to 60% of the cross-sectional area, with the lateral space being

significantly larger and containing more muscle fibres than the medial space.^{5,19}

Several studies have investigated differences in the proportion of muscle fibres in the SL with age, breed, sex and region; however, there is little agreement in the literature. Initial studies reported no change in muscle content with ageing,²⁰ and other studies have not reported horse age.⁵ However, a more comprehensive study found a significant decrease in muscle content, as well as adipose tissue with ageing, with a concomitant increase in connective tissue content, although it should be noted that this study was conducted in standardbreds and so findings may not be applicable to other breeds.²¹ In young Thoroughbreds, high intensity training resulted in a significantly higher collagen content in the SL compared with horses exercised at low intensity.²² Indeed, breed specific differences in SL muscle content have also been reported, with 40% greater muscle area in standardbreds compared with Thoroughbreds, and while female standardbreds have a greater SL muscle content than males, there are no sex differences in Thoroughbreds.^{20,21} Further, standardbred hindlimb muscle area content within the SL is greater than in the forelimb; however, this is not the case in the Thoroughbred.²⁰

Differences in muscle fibre orientation in the SL have also been reported, with parallel muscle fibres in the proximal forelimb SL which become angled more distally, whereas those in the hindlimb remain parallel throughout the ligament.^{5,19} By contrast, another study reported that muscle fibres in the SL inserted onto their neighbouring collagen fibres at an acute angle; however, it is not clear whether this was throughout the ligament or confined to a specific region.²³ The functional consequences of differences in muscle content and orientation are yet to be determined but may be related to injury predisposition. Indeed, the muscle fibre types found in the SL are predominantly type I slow twitch fibres which have a short fibre length and high pennation angle, suggesting the ability to generate a large amount of force while producing little work.²³ This implies that the muscle fibres actively contribute to stabilisation of the forelimb during locomotion, and therefore the high variability seen may affect SL function.

The interfascicular spaces of the SL also house vascular and neural components, with blood supplied proximally from the medial and lateral palmar/plantar arteries, and palmar/plantar metacarpal/tarsal arteries. The blood to the distal SL is also supplied by the lateral and medial palmar/plantar digital arteries.²⁴ The SL has an extensive microvascular network throughout its length, with multiple arterioles and venules present not only in the interfascicular spaces but also within the bundles of collagenous fascicles.²⁴ This is in contrast to the SDFT, which has a relatively avascular zone that is prone to injury,²⁵ suggesting that lack of blood supply does not contribute to increased risk of injury to a particular region of the SL.

The innervation of the SL is relatively well characterised, largely due to work undertaken to understand the nerve supply for diagnostic and treatment purposes, discussed later in this review. The forelimb SL receives its innervation from the deep branch of the lateral palmar nerve (DBLPN), which contains fibres from both the ulnar and median nerve.^{26,27} Similarly, in the hindlimb, the SL is innervated by the deep branch of the lateral plantar nerve, which is a branch of the tibial

nerve.²⁸ There can be anatomical variations in the DBLPN, with the number of ramifications entering the SL ranging from 2 to 6, and the relationship between the DBLPN and surrounding structures, including the deep plantar arch and accessory ligament of the deep digital flexor tendon (DDFT) also varies.²⁹ While this is unlikely to have implications for normal function, it does have important consequences for denervation-based treatments for SL injury, as discussed below. Nerve fibres are found throughout the SL, particularly in the interfascicular spaces in which the presence of neurovascular bundles have been described.¹⁹

Little attempt has been made to characterise cell populations within the SL, and even cell nomenclature is not well defined, with cells referred to as fibroblasts, ligamentocytes or desmocytes.^{30–32} Studies have measured the DNA content of the SL, which gives a measure of cell number, and varies along the length of the ligament, increasing from proximal to distal.⁵ SL DNA content is also greater than in the SDFT and DDFT,³³ (Table 1) suggesting a more cellular structure. In addition, there is a very similar gene expression profile between the SL and SDFT, likely reflecting their similar roles as energy stores. However, there are some differences between structures, with lower expression of fibromodulin, MMP-3 and -10 in the SDFT

TABLE 2 Gene expression profile of SL and SDFT.

| | Superficial digital flexor tendon | Suspensory ligament |
|--------------|-----------------------------------|---------------------|
| Col1A2 | 34.93 ± 40.90 | 29.58 ± 27.21 |
| Col3A1 | 18.56 ± 22.23 | 19.06 ± 24.95 |
| Col5A1 | 1.49 ± 2.26 | 0.69 ± 0.85 |
| Col12A1 | 9.51 ± 7.81 | 15.52 ± 24.32 |
| Aggrecan | 5.55 ± 10.24 | 3.95 ± 4.53 |
| Biglycan | 63.27 ± 77.84 | 75.65 ± 170.55 |
| Decorin | 1343.42 ± 1713.18 | 763.11 ± 429.75 |
| Fibromodulin | 32.80 ± 37.79 | 13.28 ± 12.39* |
| Lumican | 48.50 ± 42.14 | 58.21 ± 47.97 |
| MMP-1 | 0.03 ± 0.06 | 0.01 ± 0.06 |
| MMP-3 | 3.52 ± 4.70 | 0.70 ± 1.58** |
| MMP-9 | 0.43 ± 1.13 | 0.84 ± 1.70 |
| MMP-10 | 17.46 ± 25.34 | 2.23 ± 4.36*** |
| MMP-13 | 0.16 ± 0.68 | 0.03 ± 0.06 |
| MMP-23 | 0.03 ± 0.06 | 0.03 ± 0.06 |
| TIMP-3 | 55.08 ± 52.55 | 48.69 ± 53.51 |
| TIMP-4 | 0.53 ± 0.85 | 0.64 ± 0.74 |
| ADAM-12 | 0.05 ± 0.06 | 0.03 ± 0.06 |
| ADAM-17 | 1.21 ± 1.24 | 0.90 ± 1.02 |
| ADAMTS-2 | 1.22 ± 1.53 | 0.63 ± 0.85 |
| Tenascin | 1.86 ± 2.77 | 1.15 ± 1.70 |
| Scleraxis | 3.79 ± 5.60 | 2.51 ± 3.00 |
| COMP | 2674.33 ± 3255.43 | 2111.21 ± 1898.04 |

Note: For further details of methodology see Thorpe.¹⁰ Significant differences between tissue types are indicated by *: **p* < 0.05; ***p* < 0.01; ****p* < 0.001. Data are shown as mean ± SD. *n* = 32.

compared with the SL.³³ There were no significant differences in gene expression with ageing in the SL (Table 2).

While some studies have investigated cell behaviour in vitro, the focus of this research has been to develop treatments rather than understand fundamental cell biology.^{30,34–36} With recent single cell sequencing studies in tendon unveiling the complex cellular heterogeneity within these tissues,^{37–39} it is important that future studies identify, characterise and localise individual cell populations within the SL to understand the role of each population in ligament health, ageing and disease.

2 | SUSPENSORY LIGAMENT MECHANICAL PROPERTIES

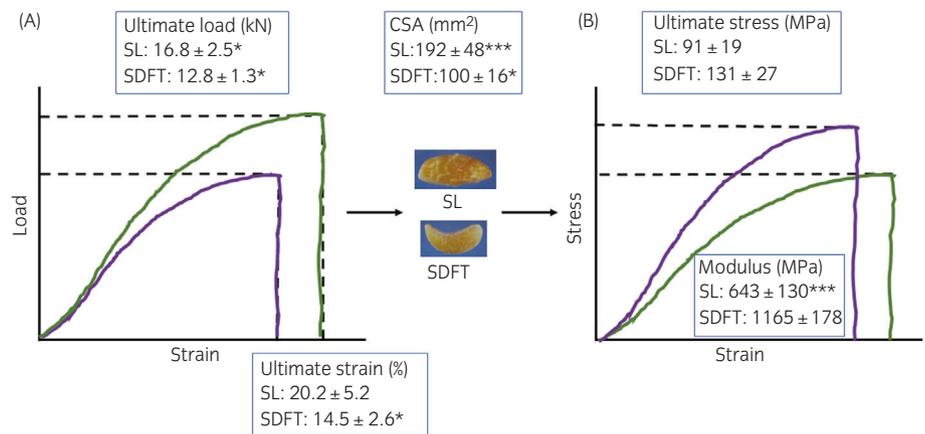
The mechanical properties of the SL have also been investigated, although these remain less well defined than those of the distal limb tendons. Mechanical testing of the entire SL revealed large differences in regional strain patterns under loading, with greater strains in the branches compared with the mid-body and proximal regions. There were also differences in strain response within the mid-body, with the distal region experiencing higher strains than the proximal region.⁴⁰ This is supported by studies that have mechanically tested small sections of the SL, and shown that strain is significantly greater in the branches of the ligament than in the mid-body, while elastic modulus and stiffness are significantly lower.⁵

Mechanical testing of the body of the SL suggests a more compliant tissue than the SDFT. Data from our laboratory (unpublished) shows that the elastic modulus is significantly lower than the SDFT (Figure 3). The ultimate strength of the SL is higher than the SDFT, as expected for a larger structure; however, the ultimate stress is significantly lower (Figure 3).

The forces and strains experienced by the SL in vivo have also been determined by implanting transducers within the ligament. Strains of ~3.5% were measured in the walk, increasing to ~5.5% in the trot. There was also an effect of ground surface, with greater strains on pavement than sand.⁴¹ SL strains are also affected by shoeing, with increased strains when heel wedges or egg-bar shoes were applied compared with a neutral shoe.⁴² In support of in vitro data, transducer-measured strains within the SL branches are higher than in the body, reaching ~5.4% at the walk and ~9.1% at the trot.⁴³ However, transducer implantation results in alterations in SL mechanical properties in the days following implantation, reducing stress and strain measured post-mortem.⁴³ Further, as transducer implantation is highly invasive, this technique is no longer considered an acceptable method for measuring tendon and ligament strains.

More recently, noninvasive modelling approaches have identified that the forces and strains experienced by the SL peak during mid-stance, with maximum force and strain exceeding 11 kN and 20% respectively during trotting.^{44–46} These strains are higher than those measured in vivo, which may be due to overestimations as a result of the modelling parameters used.⁴⁴ There are also differences in strain between limbs, with higher strains in the forelimb SL, increasing to over 30% in the gallop, whereas strains in the hindlimb remain similar to

FIGURE 3 Stylised force/elongation curve (A) and stress–strain curve (B) for SL (green) and SDFT (purple) overlaid with data obtained *in vitro* from experimental measurement of mechanical properties. Data are shown as mean \pm SD ($n = 6$). Significant differences between structures are indicated by *: $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.



those in the trot.⁷ Speed within a pace will also likely affect SL loading environment, with greater tarsal flexion and metacarpophalangeal joint extension measured in extended trot compared with a collected trot presumably leading to greater SL strains.⁴⁷ Strains in the SL can also vary according to abrupt changes in ground surface, suggesting that surface inconsistency may contribute to increased risk of injury.⁴⁸

The effect of training on SL morphology and composition has also been studied, with no differences in SL cross-sectional area between trained and untrained horses.^{49,50} However, collagen content in the SL is increased and GAG content is decreased in high intensity compared with low intensity training.²² This may indicate an accelerated loss of muscle tissue within the SL as a result of high intensity exercise. The limited changes in SL properties post-training suggest that this structure is already highly optimised for efficient function, and little enhancements can be gained through conditioning.

3 | EPIDEMIOLOGY OF SUSPENSORY LIGAMENT INJURY

The majority of research into the epidemiology of SL injury has been in the Thoroughbred racehorse. In this population, SL injuries are common with an incidence of 2.7 per 1000 horse starts,⁵¹ and a prevalence of 3.6%–10%.^{52–54} Although SL injuries represent a significant proportion of all injuries (11.5%–21.5%), they occur less frequently than bone fractures and injury to the SDFT.^{51,55} In racehorses, 89% of tendon and ligament injuries are to the SDFT and 11% are to the SL.⁵⁶ This may be why, compared with bone fracture and tendon injury, limited research has been performed to identify risk factors for SL injury in racing Thoroughbreds.

Horses with subclinical to mild injury of the SL ligament are more likely to develop a severe injury.⁵⁷ Abnormality of the SL detected during a prerace physical inspection was associated with an increased risk of injury during the race.^{58,59} Further, horses suffering from an SL injury prior to the start of their 2-year-old race season have a decreased racing ability.⁵⁴ Given that up to 68% of Thoroughbred horses will not race again after sustaining an SL injury,⁶⁰ a better understanding of the risk factors predisposing to SL injury would be of benefit.

Several studies have demonstrated an association between age and SL injury.^{57,61} Two-year-old horses have less SL desmitis than older horses,⁶⁰ the risk of SL injury in 3- and 4-year-olds is around twice as high than in 2-year-olds,⁵³ and horses over 5 years old have a five times higher risk of SL injury than 2-year-olds.⁵³

Other factors associated with risk may include sex, as entire males have been found to be at greater risk in one study.⁵³ Whereas another study found a significant association of SL injury and trainer but not gender.⁵⁶ The race type may influence risk, with increased numbers occurring in chases rather than flat racing and on all-weather tracks compared with turf.⁶¹ By contrast, no seasonal association with SL injury has been observed.⁵¹ An association between mild SL injuries and both the height of shoe toe grabs and distance trained in the preceding week has been found.⁵⁷ Likewise, horses that had undergone a superior accessory ligament desmotomy to treat an SDFT injury were at 5.5 times greater risk of developing SL injury than horses managed nonsurgically.⁶² These findings suggest that changes to load distribution and exercise may influence the risk of an SL injury.

SL injury is also a significant problem in other breeds and horses competing in other disciplines. In standardbred racehorses, SL injury is the most frequent musculoskeletal injury,⁶³ whereas in racing Arabians and Thoroughbreds, SDFT injury is more common.⁶⁴ SL injuries are reported in horses used in barrel racing, although they are less common than foot pain and osteoarthritis.⁶⁵ In event horses, SDFT injuries are more common than SL injuries,^{66,67} whereas in general purpose horses, showjumpers and dressage horses the SL is the most commonly injured site.⁶⁶ Interestingly, dressage horses have more hindlimb SL injuries,⁶⁸ whereas it is predominantly the forelimb SL which is affected in all other disciplines.⁵³ This may reflect the increased weight bearing undertaken during collection and more advanced dressage movements which result in increased loading on the hindlimbs.⁶⁸

In other breeds and disciplines, there are fewer studies reporting the return to work and re-injury rates following an SL injury than in racehorses. In one study, only up to 25% of Dutch Warmblood horses and 18% of Standardbreds showed full-functional recovery.⁶⁹ However, another study found that following an apical fracture, 56%–88% of Standardbreds returned to racing, and this was not affected by the

degree of associated SL damage.⁷⁰ In leisure horses with SL branch injuries, 24% returned to the same level of work 2 years after injury, with 41% of horses returning at a lower level of work, and the remainder being unable to return to a ridden career.⁷¹

Therefore, while it is clear that SL injuries are a major problem across multiple disciplines, very few specific risk factors have been identified.

3.1 | Aetiology and pathophysiology of suspensory ligament injury

Following injury to the SL relatively little is known about what happens to the SL matrix or cellular components. Histological studies have reported changes in collagen fibre organisation and fibroblast viability.^{72,73} Ultrasonography has also revealed mineralisation in the SL branches, although this is not always associated with lameness.⁷⁴

While most SL injuries occur in the absence of any underlying condition or known genetic variation, there are certain disorders that can directly affect the SL and therefore predispose to injury. Indeed, a significant heritability of 0.05 to 0.17 has been reported for SL injury in Thoroughbreds in Hong Kong,⁵² suggesting a genetic component to injury risk. Furthermore, the SL is affected in some heritable conditions. For example, Quarter horses suffer from an autosomal recessive condition, Hereditary Equine Regional Dermal Asthenia (HERDA). Affected homozygous horses have fragile and hyperextensible skin, which makes the horses unsuitable for riding. However, the ultimate tensile strength of the SDFT, DDFT and SL are also significantly reduced.⁷⁵ An increased risk of SL injury has not been reported in these horses, but this may be due to their inability to undertake ridden work.

Degenerative suspensory ligament desmitis (DSLDD) is a chronic, progressive disease that occurs in a range of breeds with an estimated heritability of 0.22.^{76,77} Affected horses usually develop bilateral or quadrilateral lameness and do not improve with rest.⁷⁸ In addition to the SL, other tissues are also affected.^{79,80} The disease is characterised by collagen fibre disorganisation and increased proteoglycan accumulation and is also known as equine systemic proteoglycan accumulation (ESPA).^{79,80} Specifically, increases in aggrecan, aggrecanases, such as ADAMTS4 (A-disintegrin-and-metalloproteinase-with-thrombospondin-like-motifs 4) and ADAMTS5, and $\alpha 1$ (inter-alpha-trypsin-inhibitor, a marker of chronic inflammation) have been observed in affected SLs.⁸¹ An abnormal isoform of decorin that has reduced binding to TGF- $\beta 1$, has also been found to accumulate in affected tissues. This is associated with increased TGF- $\beta 1$ expression that may affect collagen turnover.⁸⁰ Altered TGF- β -signalling target genes have also been reported in cells from affected horses.⁸² Increased levels of BMP2 have also been reported in SLs and skin from affected horses.^{83,84} Recent work has suggested that DSLDD is a polygenic disease,⁸⁵ but causal variants have yet to be identified. A genome-wide association study showed enrichment of pathways associated with ECM homeostasis, proteoglycan metabolism and hedgehog signalling.⁷⁷ It is likely that DSLDD is a complex disease with

additional risk factors, for example, an association between DSLDD and pituitary pars intermedia dysfunction (PPID) has been reported.⁸⁶ This may be due to dysregulation of cortisol metabolism.⁸⁷ The link between endocrine disorders and SL injury therefore warrants further investigation.⁸⁸

Injury to the SL has also been associated with injuries to other musculoskeletal tissues. For example, partial transection of the medial branch of the SL increases the strain on the MC3 lateral condylar bone surface in vitro,⁸⁹ suggesting that SL injury may increase the risk of lateral condylar fracture. Indeed, moderate lesions in SL branches are associated with an increased risk of suspensory apparatus failure and metacarpal condylar fracture.^{57,90} Magnetic resonance imaging (MRI) has also revealed that most horses with SL pathology have cortical bone pathology.⁶⁸ Equally, all cases of fatal fracture to the proximal sesamoid bones, third metacarpal or condyles had partial or complete lacerations of the SL,⁹¹ and at least 70% of horses with splint bone fractures had desmitis of the SL.⁹² Furthermore, sesamoiditis in yearlings leads to a five times greater risk of a SL branch injury when they commence training.⁹³ Sesamoiditis is also associated with subclinical ultrasonographical changes in the SL branch.⁹⁴ Damage to the SL can also occur in the presence of an exotosis on the palmar or plantar cortex of MC3 or third metatarsal (MT3) bone.⁹⁵ However, no association was observed between exotoses on the dorsoproximal aspect of MT3 and SL damage.⁹⁶

Therefore, despite the high frequency of SL injuries and their association with other MSK injuries, there is a paucity of studies to identify the causal mechanisms and the changes to the matrix and cellular components that occur following an injury.

3.2 | Diagnosis of suspensory ligament pathology

Diagnosis of SL pathology is complicated by the inaccessibility of the SL for palpation and lack of localising signs; while acute injuries may be hot with slight swelling and pain on palpation, chronic injuries do not display these signs.⁹⁷ Therefore, SL injury is usually diagnosed by a combination of diagnostic anaesthesia (nerve blocking) and imaging.

When considering the application of nerve blocks, localising pain originating from the SL can be complex due to anatomical variations in nerve supply and the presence of surrounding structures in close proximity, particularly in the proximal region, which may result in inadvertent infiltration of the carpal or tarsal joints and sheaths.^{29,98–100} In the hindlimb, anaesthesia of the DBLPN can also abolish pain originating from more distal structures in the limb, including the tarsal joint.¹⁰¹ More recent studies have refined diagnostic analgesic techniques, demonstrating that a single small volume injection adjacent to the DBLPN in the hindlimb is sufficient to provide anaesthesia to the SL; however, the risk of affecting surrounding structures remains.^{102,103} In the forelimb, direct synovial communications between the carpometacarpal joint and the proximal SL have recently been identified,¹⁰⁴ explaining why specific analgesia of the SL remains challenging. These findings highlight the importance of combining diagnostic anaesthesia with imaging for a definitive diagnosis of SL pathology.

Several imaging techniques are used to diagnose SL pathology, with the most common being ultrasound, and more recently MRI. Several abnormalities within the SL are visible on ultrasound, including enlargement, loss of definition of ligament margins, hypoechoic regions (either well or poorly defined) and areas with a diffuse reduction in echogenicity in the proximal SL (Figure 4A).^{97,107} Lesions within SL branches are also detectable ultrasonographically, appearing as anechoic zones, with hypoechoic regions, generally accompanied by heterogeneous echogenicity and disrupted fibrillar pattern.^{108,109} Indeed, ultrasonography of nonlame horses revealed that ~7% of Thoroughbreds used for flat racing, ~30% of National Hunt horses, 58% of showjumping Warmbloods and 20% of working Quarter

Horses had evidence of abnormalities in the SL branches.^{110–113} While only 5% of the showjumpers with SL abnormalities went on to develop clinical signs of SL branch injury within 1 year, more comprehensive studies are required to fully establish if these subclinical abnormalities predispose to injury.

There can be significant inter-operator variability during ultrasound assessment of the SL, particularly in the proximal region, which should be taken into consideration when diagnosing SL disease.¹¹⁴ Ultrasound imaging of the proximal SL is also complicated by the presence of muscle and fat within this region, and therefore an in-depth knowledge of SL anatomy combined with multiple ultrasound approaches is required for accurate diagnosis.²⁸ In addition to imaging

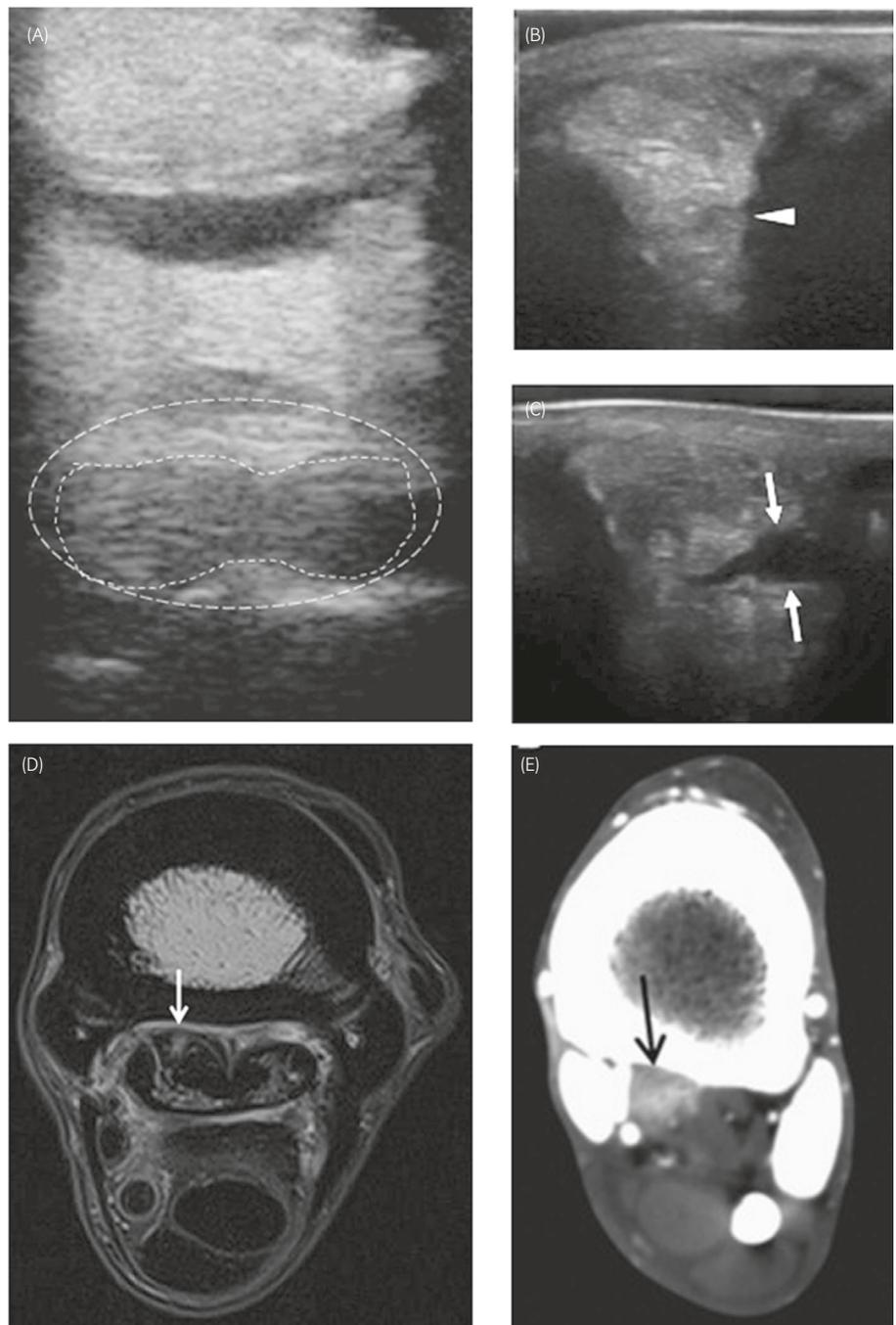


FIGURE 4 Imaging modalities used to diagnose pathology within the SL. Sagittal ultrasound image of the proximal forelimb SL showing a focal hypoechoic region with fibre disruption (A). Longitudinal ultrasound of the lateral forelimb SL branch performed under weightbearing (B) and nonweightbearing (C). Note the split which is markedly more apparent during nonweightbearing examination. MRI of the proximal forelimb showing a focal injury to the medial lobe of the SL (D). Contrast enhanced CT image of the proximal hindlimb demonstrating enlargement of the SL accompanied by increased contrast (E). Images adapted from Gaschen et al.,¹⁰⁵ Werpy et al.¹⁰⁶ and Werpy and Denoix²⁸ with permission from the publishers.

from the palmar aspect of the limb, it is recommended that medial and lateral imaging is performed to detect lesions on the edge of the SL, along with examination using the angle contrast technique with the limb slightly flexed and nonweightbearing, enabling visualisation of the origin of the SL and ability to distinguish collagen fibres from muscle and fat.^{28,115} Indeed, this nonweightbearing technique is also successful at visualising longitudinal splits in the SL branches which are not visible when the horse is bearing weight (Figure 4B,C).¹⁰⁶ This approach has been used to identify an increase in SL abnormalities between 2- and 4-year-old Quarter horses used for cutting.¹¹⁶ Doppler ultrasonography, which provides the ability to detect increases in blood flow, has also been investigated as a diagnostic tool for SL disease, with studies showing good agreement between Doppler and B-mode ultrasonography when assessing pathology in SL branches.¹¹⁷

Another recently developed ultrasound-based technique is elastography, which is able to estimate tissue stiffness with good reliability and repeatability between operators when imaging normal SLs.¹¹⁸ In addition, elastography of pathological SLs showed that acute lesions were softer than chronic lesions, and stiffness increased with healing. Elastography therefore has the potential to improve characterisation and monitoring of SL disease; however, elastography was unable to detect some small, proximal lesions,¹¹⁹ limiting its applicability for diagnosis of injuries in this region. Elastography is also yet to be used for clinical diagnosis of SL disease in the horse.

While these ultrasound-based techniques are successful in identifying a high proportion of SL injuries, MRI provides advances in early diagnosis of SL injuries (Figure 4D),²⁸ which is likely key for successful treatment. Development of MRI units able to accommodate a horse limb has provided significant advances in imaging of the SL, with initial studies on disarticulated limbs demonstrating an excellent ability to resolve distal limb structures including the SL.¹²⁰ Studies comparing MRI and ultrasound with histology of the normal SL showed that MRI was able to detect the interfascicular spaces present within the ligament, which could not be resolved using ultrasound.^{2,19} MRI of nonlame horses also demonstrated large variability in appearance of the SL, particularly in the proximal region, which should be taken into account during image interpretation.¹²¹ Changes detectable on MRI include SL thickening, adhesions between the SL and adjacent bony structures, loss of fibre integrity and the presence of core lesions.^{105,122} MRI is also able to detect biochemical changes in the absence of overt structural changes, leading to earlier diagnosis and potentially improved prognosis¹²³; however, it is important that normal variations are not mis-interpreted as pathology.¹²⁴ MRI is particularly useful for diagnosis of proximal SL disease, with different weightings allowing resolution of structures often difficult to visualise on ultrasound or x-ray, including the abaxial margins of the SL.¹²⁵ Indeed, direct comparison of ultrasonography and MRI for diagnosis of SL disease revealed that sonography had fair sensitivity but poor specificity in the proximal region of the ligament.¹⁰¹ MRI also provides increased sensitivity when diagnosing suspensory branch injuries, with only one quarter to half the lesions visible by MRI detectable ultrasonographically.^{126,127}

As well as enabling better diagnosis of lesions within the SL, MRI is able to simultaneously detect pathologies involving other structures, with diagnosticians considering MRI most useful in these cases

compared with those only involving the SL.^{28,128} Osseous contusions or sclerosis of the palmar cortex of MC3 at the SL origin can be a feature of SL disease, and the degree of resorption of the palmar cortex correlated with degree of sclerosis and severity of irregularity in the margin of the SL.^{123,129} MRI can also detect adhesions between exostoses on MC3 and the suspensory ligament, which are otherwise only detectable during surgery.¹³⁰ Other studies have identified the presence of bone marrow lesions within MT3 at the SL origin associated with enlargement of the SL and proximal SL pathology.^{131,132} It is interesting that irregularities in the dorsal margin of the SL and sclerosis of the MC3 have also been observed in contralateral, control limbs, which may indicate that these changes are not necessarily indicative of pathology, or conversely that subclinical abnormalities are present in the contralateral limb of horses diagnosed with SL disease in the opposite limb.¹³³ Bony abnormalities associated with SL pathology and mineralisation of SL body and branches have also been diagnosed using computed tomography (CT).^{134–136} In addition, CT can detect enlargement of the SL itself, and, when combined with injection of contrast agent, can visualise changes in blood flow within the ligament,^{28,136} indicating that CT may be a useful diagnostic tool when MRI facilities are not available (Figure 4E).

Nuclear scintigraphy is another imaging approach that has been used to detect SL pathology, with scintigraphy used in combination with radiography to diagnose avulsions of the origin of the SL.¹³⁷ Scintigraphy has been used with ultrasound to localise lameness when nerve blocks are unsuccessful,¹³⁸ but may not detect SL pathology in all cases.¹³⁹

A large body of work has been undertaken to establish the most effective technologies and protocols for accurate diagnosis of SL pathology. Ultrasound remains the mainstay of diagnosis in the field, while MRI provides increased sensitivity and early diagnosis and so should be considered in the absence of any abnormalities present ultrasonographically. Other imaging techniques such as CT and scintigraphy have also been used to diagnose SL disease, generally alongside other imaging modalities rather than in isolation.

3.3 | Treatment of suspensory ligament injuries

The standard treatment for an SL injury is box rest and controlled exercise. Modifications to shoeing are also often performed following an SL injury. Toe wedges reduce the strain placed on the SL,¹³⁹ and a wide toe and narrow branches redistribute the pressure from the toe to the heels.¹⁴⁰ However, these adaptations may increase the strain in other structures in the distal limb.¹⁴¹

As re-injury of the SL following conservative management is common, this has driven the development of other techniques to try to improve tissue healing and result in better outcomes.

3.3.1 | Surgical techniques

Surgical interventions to remove damaged tissue have been used for injuries to the SL branches,¹⁴² but large-scale studies are lacking.

Desmoplasty (surgical splitting of the injured SL) following proximal SL desmitis has been performed for horses with chronic lameness with all horses returning to work,¹⁴³ but long-term follow-up was not performed. Ligament splitting has also been combined with microfracture in experimental models of proximal SL injury,¹⁴⁴ but there are no clinical reports using this approach.

The most common surgical intervention is neurectomy. It has been proposed that proximal SL desmitis of the hindlimbs can lead to compression and damage of the DBLPN.¹⁴⁵ Neurectomy of DBLPN is effective in many chronically lame horses,¹⁴⁶ with reports demonstrating that 43%–78% of horses return to their previous, or higher, level of work.^{147–149} The variation in success may be related to discipline and other factors such as conformation.¹⁴⁹ The resolution of lameness may be due to relieving pain in the SL itself, or neuropathic pain caused by compression of the DBLPN by the inflamed SL. Although neurectomy does not lead to changes in the size of the SL,¹⁴⁷ histological studies have revealed that it does result in muscle atrophy of the proximal SL,^{150–152} which may predispose it to re-injury. Although neurectomy is widely used, there are no reports on the long-term re-injury rates following the procedure. As it may cause limb hyposensitivity, neurectomy may also restrict the competition use of the horse depending on the rules of the associated regulatory body.

3.3.2 | Extracorporeal shock wave therapy

Extracorporeal shock waves (ESWs) are pulses of high-energy pressure waves that are used in both human and veterinary orthopaedics. Early studies on the use of ESW for SL injuries demonstrated possible improvements in return to work rates in sport/general use horses, although these studies lacked control groups and compared outcomes to other published clinical data.^{153,154} A comparison of ESW therapy and platelet-rich plasma (PRP) in the treatment of Western performance horses revealed that horses treated with ESW were more likely (3.8 times) to return to work than horses treated with PRP.¹⁵⁵ In humans, ESW has been reported to have an immediate pain relieving effect but this was not found to be significant in horses with chronic proximal suspensory desmitis.¹⁵⁶

Experimental studies using collagenase-induced SL injuries revealed significant improvements in ultrasound parameters including lesion size, fibre alignment score and echogenicity in ESW-treated SLs compared with untreated controls.¹⁵⁷ However, histologically there was only a difference in metachromasia, which appeared more focal in the ESW-treated SLs, with no differences in cellular appearance or collagen III staining.¹⁵⁷ ESW therapy also significantly decreased the size of an experimentally induced lesion and resulted in significantly more small collagen fibrils along with increased TGF- β 1 expression.¹⁵⁸ However, the effect of ESW therapy on the normal, healthy SL revealed that 6 weeks after treatment there was a decrease in GAG and collagen synthesis while overall DNA content remained unchanged.¹⁵⁹ The tissue also appeared more disorganised with increased MMP14 and collagen I gene expression.¹⁶⁰

Therefore, despite some promising clinical and experimental results, the effect of ESW therapy on healthy and injured SL matrix and cellular components remains unclear.

3.3.3 | High-power laser and ultrasound-based therapeutics

High-power laser is often used in human sports medicine with the belief that it improves healing and reduces pain. In 150 sport horses suffering from tendon and SL injuries laser therapy was found to be safe and treated horses exhibited an overall re-injury rate of ~20%.¹⁶¹ However, without a control group and given the variation in the initial injury type it is not possible to draw conclusions on the efficacy of the treatment.

Using a model of SL branch injury, where lesions were created mechanically in 12 warmblood horses, lesions treated with laser therapy were significantly smaller than control lesions and showed a significantly increased Doppler signal during the treatment indicating more blood flow.¹⁶² Laser-treated lesions also showed improved histological scores and lower levels of collagen type III expression.¹⁶³ However, the mechanical properties of the tissue were not assessed.

There is also a single study reporting the use of low-frequency ultrasound in the treatment of 23 horses with SL injuries.¹⁶⁴ Eighty-seven percent of the horses returned to work, but re-injury rates were not reported and no control group was used. Another ultrasound-based technique that has been investigated for the treatment of SL pathology is percutaneous ultrasonic debridement; 3 horses that underwent this procedure had improved lameness scores and all returned to work.¹⁶⁵ However, the small sample number and lack of a control group in this single study means that this technique requires further validation as a therapeutic for SL injury.

3.3.4 | Platelet-rich plasma

Biological therapies to aid tissue regeneration by boosting cell number and/or activity have become increasingly popular over the past 20 years. In addition to their role in blood clotting, platelets release a wide variety of growth factors that may aid tissue regeneration. Increasing platelet concentrations to create PRP is relatively simple and it has therefore been a popular treatment for treating tissue injuries. However, there are few reports that have determined the effect of PRP on SL injuries.

In vitro, PRP affects gene expression in cultured SL cells with an increased ratio of collagen type I to collagen type III, increased cartilage oligomeric matrix protein (COMP) and decreased MMP-13.³⁵ Furthermore, SL tissue explants cultured with PRP have reduced IL-1 β and increased IL1Ra production.³⁴ While this is suggestive of beneficial changes, larger-scale analyses using global gene expression profiling or proteomics have not been reported.

In vivo, PRP injected into lesions in three horses with chronic SL injuries did not result in ultrasonographic improvements, but the

horses were able to return to their pre-injury level of work after 6 months, with no injury recurrence within 20 months.¹⁶⁶ In contrast, a larger study treated 11 horses with acute suspensory branch injuries with PRP. Although they found all the lesions improved ultrasonographically, only five of the horses returned to their previous level of work.¹⁶⁷ In racehorses, nine Standardbreds with SL injuries were all able to return to racing following PRP treatment. However, compared with noninjured horses they had significantly reduced earnings per start during the first year after returning to racing and a significant reduction in the number of starts in the third year.¹⁶⁸ Further, control groups were not used in any of these studies and long-term re-injury rates were not recorded.

A later study reported that PRP treatment of yearling Thoroughbreds with sesamoid bone inflammation and SL branch injuries resulted in no significant differences in money earned and races started between horses treated with PRP and control horses treated with saline.¹⁶⁹ More recently, a larger study on sports horses, involving 22 control horses and 46 horses treated with PRP for chronic hindlimb suspensory desmopathy, found that significantly more horses treated with PRP returned to their previous level of activity compared with the controls.¹⁷⁰ However, 25 horses in a third group were treated with concentrated bone marrow aspirate and these horses were found to have better lameness scores than the PRP-treated group at both short- and long-term follow-up.¹⁷⁰

3.3.5 | Bone marrow and stem cell-based therapies

Acellular bone marrow aspirate has also been investigated for its therapeutic use. However, these studies have only been performed *in vitro*. Acellular bone marrow added to cultured ligament fibroblasts was found to increase COMP and total protein synthesis to a greater degree than PRP.³⁰ It was also found to stimulate decorin and COMP gene expression by SL explant cultures to a greater degree than PRP.³⁶ Nevertheless, it is considerably more invasive to derive than PRP and the effect of using acellular bone marrow alone to treat SL injuries in horses has not been reported.

Whole bone marrow aspirate containing the cellular and acellular fractions was used to treat forelimb SL injuries of 13 Standardbred and 17 Thoroughbred horses. Approximately 70% of both groups returned to racing and had 5 or more starts.¹⁷¹ Similarly, a combination of PRP and bone marrow mononuclear cells was used to treat 13 horses with either SL or SDFT injuries and 84.6% returned to work.¹⁷²

These early promising results led to work that focussed on the mesenchymal stromal/stem cells (MSCs) present in the bone marrow and other tissues. Umbilical cord blood (UCB)-MSCs were used to treat 22 warmblood horses with SL injuries, of which 68% returned to work.¹⁷³ A more recent study treated Thoroughbred racehorses with SL branch injuries with allogeneic UCB-MSCs, followed by multiple treatments with autologous BMSCs and 71% of horses returned to racing for an average of 29.5 months.¹⁷⁴ However, none of the aforementioned studies included a control group or assessed re-injury rates.

MSCs which have been primed towards the tendon lineage (tenogenic primed MSCs) express more type I collagen and less smooth muscle actin than nonprimed MSCs and have better adherence to tendon and ligament tissue explants *in vitro*.¹⁷⁵ A case study first reported the safe application of allogeneic tenogenic primed MSCs for an SL injury,¹⁷⁶ and this was followed by a larger study which treated 68 horses with an SL injury with allogeneic tenogenic primed MSCs in PRP and found 82.4% had returned to the previous level of performance after 2 years and only 17.6% of horses had re-injured. However, while promising, there was no control group with which to compare the re-injury rates.¹⁷⁷ A recent randomised control trial comparing injection of a proprietary formulation of tenogenic primed MSCs with saline injections showed greater improvement in ultrasound and lameness scores in the MSC-treated SLs up to 112 days post-treatment. Further, follow-up after 2 years showed that re-injury rates were significantly greater in saline treated compared with MSC-treated horses.¹⁷⁸ A more recent refinement of MSC-based therapeutics focuses on microvesicles from MSCs, which are proposed to contain many of the factors that underpin MSC efficacy in aiding tissue repair. Microvesicles from adipose-derived stem cells were injected into the injured SL of one horse and no adverse events were observed.¹⁷⁹ However, no conclusions on efficacy can be made.

3.3.6 | Gene therapy

Gene therapy approaches have also been trialled as a treatment for SL injuries. Gene therapy involves the injection of expression vectors to express specific genes beneficial for tissue repair. It therefore offers a more targeted approach than the use of PRP or MSCs. The injection of a plasmid expressing vascular endothelial growth factor 164 (VEGF164) and fibroblast growth factor 2 (FGF2) under the control of constitutive promoters was performed in 10 horses with SDFT or SL injury.^{180,181} Eight of the 10 horses were able to return to work with no re-injury during the 12-month follow-up. However, only three of the horses had SL injuries and one of these did not return to work. This study also had no control group and so, while promising, limited conclusions on effectiveness can be drawn.

In summary, while many treatments are being used to treat SL injuries, there is limited data on return to work and re-injury rates. The lack of control groups, or even robust baseline data, makes it difficult to determine efficacy and further research should address this unmet need.

4 | CONCLUSIONS

It is evident that the SL in the horse has evolved into a complex and heterogeneous structure, reflecting its crucial role in supporting the distal limb and providing efficient locomotion. Despite these specialisations, the SL is prone to injury and while a variety of treatments are available, the long-term outcome of these therapeutics remains uncertain. The basic structure of the SL has been characterised, however,

studies investigating the relationships between cellular and matrix composition and function, and how these are affected by injury are lacking. This knowledge gap hampers the ability to develop novel therapeutics to effectively treat SL injury.

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Deborah J. Guest: Conceptualization; writing – original draft; writing – review and editing. **Helen L. Birch:** Writing – original draft; writing – review and editing. **Chavaunne T. Thorpe:** Conceptualization; writing – original draft; writing – review and editing.

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Data sharing is not applicable to this article as no new data were created or analysed in this study.

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