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REVIEW ARTICLE

Degenerative Suspensory Ligament Desmitis – A New Reality

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ABSTRACT

Degenerative suspensory ligament desmitis (DSLD) is a chronic, debilitating disease occurring primarily in Peruvian Pasos and Peruvian Paso crosses. However, many other breeds are afflicted as well. DSLD is characterized by a slowly progressing bilateral or quadrilateral lameness. Typically, the owner does not recall any trauma or performance related injury. Fetlock effusion, static and dynamic hyperextension and degenerative joint disease are hallmarks on physical examination. Ultrasonography of affected ligaments reveals diffuse loss of echogenicity, and an irregular fiber pattern. Though until recently DSLD was considered a collagen disorder strictly limited to suspensory ligaments (SLs), our data show that it is a systemic disease involving tissues with high content of collagen. We have identified abnormal accumulations of proteoglycans not only in the SLs, but also in the superficial and deep digital flexor tendons, patellar and nuchal ligaments, aorta, coronary arteries and sclerae of DSLD-affected horses. Our most recent data point to the presence of an abnormal form of decorin in these proteoglycan deposits. This decorin also exhibited altered biological activity. Treatment for DSLD-affected horses is empirical and directed at minimizing musculoskeletal pain and providing support for the suspensory apparatus. Restricted exercise, supportive bandages and nonsteroidal anti-inflammatory drugs provide some, but usually only temporary relief. Unfortunately, unrelenting pain, severe lameness and suffering require all too often humane euthanasia.

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INTRODUCTION

Tendon injuries are common in horses, particularly in those participating in races and competitions. The healing of tendon and ligament tissues occurs slowly. Unfortunately, the repaired tissue is inferior in elasticity and strength as compared to the original tissue. This means that up to 80% horses injured once will have at least one repeated injury or trauma (Webbon, 1973; Madison, 1995; Bramlage and Hogan, 1996; Sawdon *et al.*, 1996). The superficial digital flexor tendon is injured in 7 to 43% of race horses (Bramlage, 1986; Ross, 1997; Jorgensen and Genovese, 2003). Injuries of the deep digital flexor tendon (DDFT) occur less frequently except when associated with chronic desmitis of the accessory ligament of the DDFT (Dyson, 2003a and 2003b). Injuries of the proximal SLs are common in the forelimbs of the athletic horses (Dyson, 1988 and 1991) and lead to sudden onset and short-lived lameness, lasting usually for less than 24 hrs (Dyson and Genovese, 2003).

In contrast, proximal suspensory desmitis in the hind limb leads to poor performance and to chronic, persistent lameness, most likely due to a compartment-like syndrome and pressure on the plantar metatarsal nerves (Dyson, 2007). Traumatic suspensory desmitis has to be distinguished from so called degenerative suspensory ligament desmitis (DSLD).

DSLD has baffled, at least in the US and South America, many horse breeders, horse owners and veterinarians in recent years, because it occurs, usually in certain breeds, without a prior warning, i.e., in the absence of trauma. Until recently it has been considered a primarily disease of collagen fibrils, the main structural component of tendons (Mero and Pool, 2002). New findings indicate that improper glycosylation of proteoglycans, complex molecules involved in proper assembly of collagen fibrils (Yoon and Halper, 2005),

plays a role in pathogenesis of DSLD (Halper *et al*., 2006; Kim *et al*., 2010). In addition, new data show that DSLD is a systemic disease (Halper *et al*., 2006) rather than a disorder limited to SLs (Mero and Pool, 2002).

Clinical presentation and findings

Degenerative suspensory ligament desmitis or DSLD was first recognized as a distinct and separate disorder from traumatic tendon and SLs injuries by Young (1993). It was Mero and her associates who described it as a heritable, debilitating syndrome occurring primarily in Peruvian Pasos and Peruvian Paso crosses (Mero and Pool, 2002; Mero and Scarlett, 2005). However, Arabians, American Saddlebreds, American Quarter Horses, Thoroughbreds, and some European breeds are afflicted with it as well (Young, 1993; Halper *et al*., 1996). Affected Peruvian Paso horses demonstrate clinical signs at an earlier age than horses of other breeds (Mero and Pool, 2002). The usual presentation of DSLD is a rather slow onset of bilateral or quadrilateral lameness which is not preceded by a trauma or performance related injury (Mero and Pool, 2002). Physical examination reveals fetlock effusion, static and dynamic hyperextension and degenerative joint disease (Young, 1993; Xie *et al*., 2010). Ultrasonography of affected ligaments typically shows diffuse loss of echogenicity and an irregular fiber pattern (Dyson, 1996; Dyson *et al*., 1995; Gibson and Steel, 2002). The diffuse enlargement of the affected ligaments despite exercise restrictions is considered a major diagnostic sign of DSLD (Young, 1993; Mero and Pool, 2002; Mero and Scarlett, 2005). The pathogenesis of DSLD is incompletely understood, though some progress has been made recently (Kim *et al*., 2010; see below in Pathogenesis). DSLD occurs in families of horses; however, a definitive heritable mechanism has not been established. No DSLD gene has been identified so far. Tentative diagnosis is based on patient signalment and history, clinical examination, and ultrasonographic examination (Mero and Scarlett, 2005), and, in some cases, on evaluation of biopsy of the nuchal ligament of clinically affected horses (Halper and Mueller, unpublished data). Only post mortem examination can give definitive diagnosis (Halper *et al*., 2006). At the present time we do not have a reliable method for diagnosis of DSLD in asymptomatic horses.

New findings indicate that DSLD is a systemic disease rather than a disorder limited to SLs. As discussed below tissues with high content of collagen, or better, extracellular matrix, might be involved in DSLD. We have detected excessive accumulations of proteoglycans not only in the SL, but also in the superficial and deep digital flexor tendons, patellar and nuchal ligaments, aorta, coronary arteries and sclerae of DSLD-affected horses (Halper *et al*., 2006).

Pathology

Until recently the pathology associated with the clinical syndrome DSLD has been thought to be the result of degeneration of collagen fibrils and fibers located in the SLs of the distal limb of horses (Mero and Pool, 2002). However, our findings indicate that the changes in collagen are secondary, and that abnormal accumulations of proteoglycan between collagen fibers are the primary pathological change in DSLD. An easy way to identify these deposits is light microscopic examination of tissues stained with standard hematoxylin & eosin. The bluish to purplish hue of amorphous acellular material is quite distinctive (Halper *et al.*, 2006). In mild or incipient cases only slight bluish hue surrounding nuclei of tenocytes is noticeable (Fig. 1B). However, with the progression of the disease this material is deposited extracellularly (Fig. 1C), and, with time, it starts first pressing and displacing collagen fibers (in tendons), elastic fibers (in ligaments and blood vessels), and in many cases it is interspaced with cartilage foci. Its color usually becomes dark blue (H&E stain) later on (Fig. 1D). Proteoglycans can be easily identified by alcian blue stain in normal tendons where the staining is usually light (Fig. 1E), and in affected tissues where proteoglycans stain with great intensity (Fig. 1F). We have also found that this excess of proteoglycans is present in other structures and organs with high content of connective tissue. In other words, DSLD is in fact a systemic disorder involving many tissues and organs with a significant content of extracellular matrix. For example, deep and superficial digital flexor tendons, patellar ligaments, aorta, coronary arteries, nuchal ligaments, and ocular sclera show histopathological changes very similar to those found in SLs (Halper *et al.*, 2006). The excessive presence of proteoglycans in blood vessels is accompanied by disruption and disorganization of elastic fibers in the media and vascularization and myxomatous transformation of cardiac valves. Electron microscopic changes show disruption of the bimodal pattern of collagen fibril distribution seen in normal tendons. The observed increase in number of small diameter fibrils in DSLD-affected tendons (Fig. 2) can be attributed to disruption of normal fibrillogenesis initiated by the excessive presence of proteoglycans (see below in Pathogenesis). Replacement of muscle bundles with proteoglycans and/or outright cartilage is a characteristic part of pathology in SLs. It is important to emphasize that all of these lesions and deposits are void of any inflammatory exudates and cells (Halper *et al*., 2006). In light of these observations, a more appropriate term for this disease process may be equine systemic proteoglycan accumulation (ESPA) which we have been using on some occasions (Kim *et al.*, 2010).

Occasionally, we see whirls of active exuberant fibroblasts in tendons from DSLD-affected horses. There is very little collagen present in such foci, but incipient proteoglycan intracellular production is usually noticeable; especially after staining with alcian blue (Halper *et al.*, 2006). We hypothesize that these proliferative lesions represent an early stage, and eventually progress to a less cellular (and finally acellular) phase characterized by increasing proteoglycan content. Typically, no inflammatory or fibrotic changes accompany deposits of proteoglycans or proliferative lesions at any stage, early or late. We hypothesize that the proliferating fibroblasts secrete proteoglycans which, as the disease progresses, then accumulate in tissues. What stimulates the proliferation of fibroblasts and the subsequent production of proteoglycans is not known. The proliferation of fibroblasts and growth of the exuberant connective tissue may explain the presence of pain in the early stage of the disease or during an acute relapse.

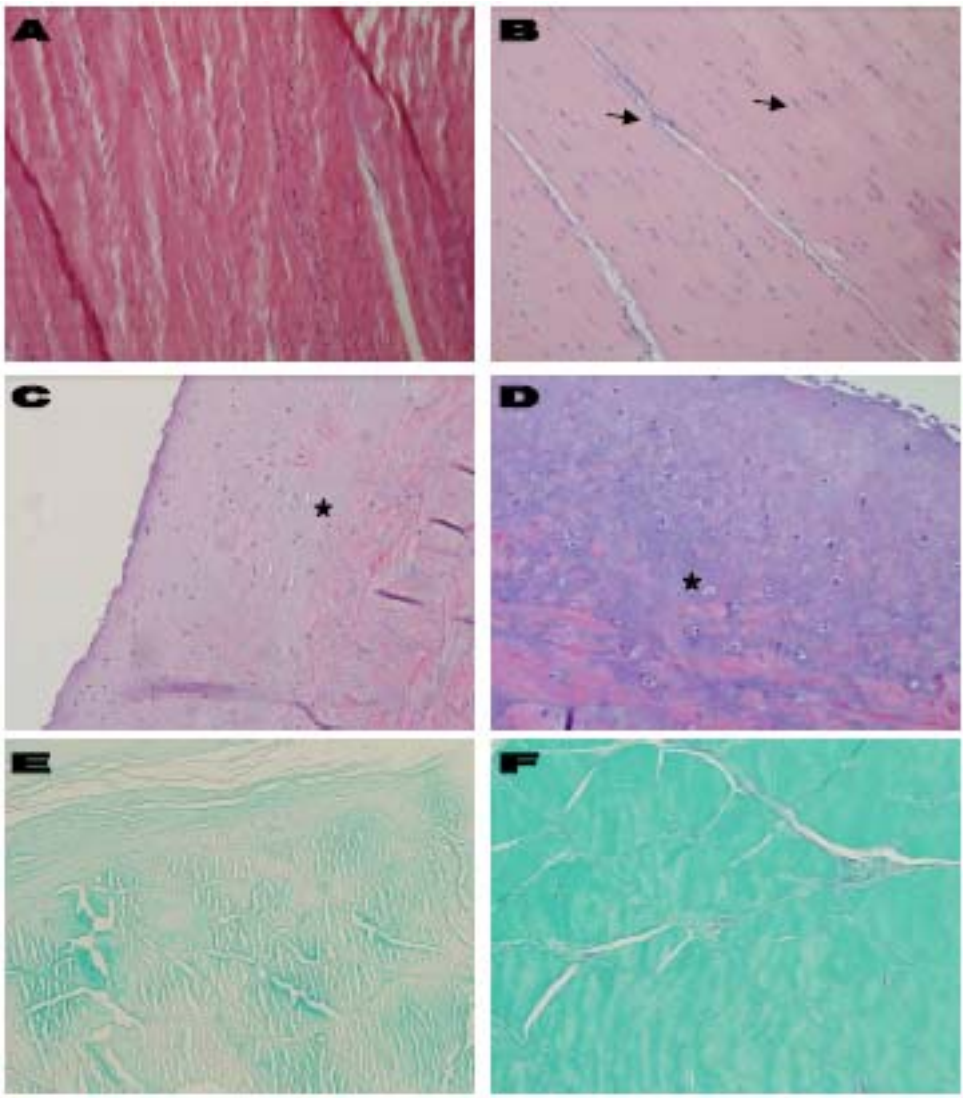

Fig. 1: (A) Control, healthy tendon stained with hematoxylin and eosin, original magnification x 200. (B) DSLD tissue, lightly infiltrated with proteoglycans (→), stained with hematoxylin and eosin, original magnification x 200. (C) DSLD tissue with heavy accumulation of proteoglycans (*) stained with hematoxylin and eosin. (D) Incipient cartilage formation in tendon heavily infiltrated with proteoglycans (*). (E) Control tendon stained with alcian blue. (F) DSLD tendon stained more intensively with alcian blue. Original magnification x 100. Portions of this figure originally appeared in Kim *et al.* (2010).

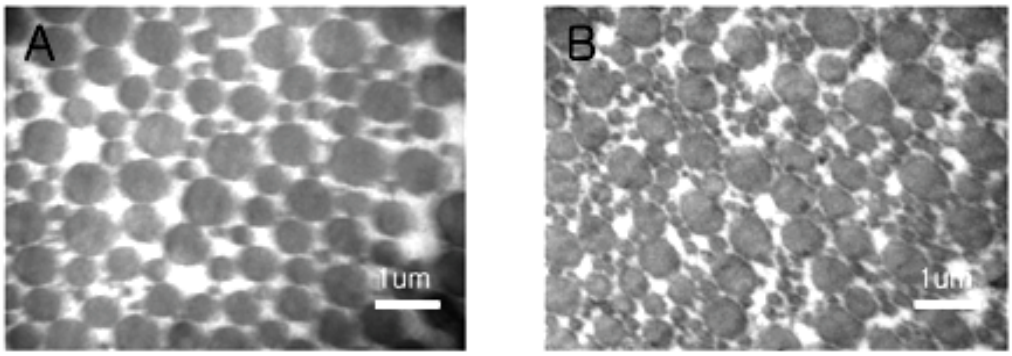

Fig. 2: Electron micrographs of normal and DSLD-affected tendon. A. A cross-section of normal tendon reveals that most collagen fibrils have fairly large diameters. B. A marked increase in small collagen fibrils was observed in cross-sections of DSLD-affected tendon. This figure originally appeared in Halper *et al.* (2006).

Miller and Juzwiak (2010) have described a case of a 3 month old foal suffering from acute rupture of SLs in the hind limbs. On necropsy they found multifocal fibrovascular proliferation with only minimal inflammation and proteoglycan accumulation. This would be similar to the proliferative lesions described above. The presence of blood vessels and inflammatory cells in their case can be attributed to the acute rupture of the SLs. Schenkman *et al.* (2009) have also observed an increased accumulation of proteoglycans in SLs and superficial and deep digital flexor tendons in DSLD, but not in other organs. However, their study was different in two aspects from ours: they evaluated only the presence of proteoglycans but no other morphological or structural changes, such as disorganization of elastic fibers in the media of aorta and coronary arteries, myxomatous transformation and vascularization of heart valves. Moreover, the use of Safranin O for visualization of proteoglycans in their study may be less than ideal as it stains preferentially aggrecan-related proteoglycans and degradation products of aggrecan (Mahmoodi *et al*., 2005) but not other proteoglycans with keratan sulfate and chondroitin sulfate chains (Camplejohn and Allard, 1988). In other words, it is possible that Safranin O does not stain most of proteoglycans in DSLD tissues which contain a lot of decorin (see below under pathogenesis).

Other authors found lesions similar to those seen in DSLD but which were present only in few tissues or organs. Arterial medial calcification with elastin fiber disorganization in multiple arteries was described in a horse as an isolated phenomenon limited to the blood vessels (Fayles-Williams *et al*., 2008). However, it is not clear whether any tendons or ligaments were examined as well. In our experience calcifications within the blood vessel walls were rare in DSLD. Several aspects make the presence of cartilaginous metaplasia in the sclera of sheep as described by Smith *et al*. (2010) different from scleral involvement in horses with DSLD: no involvement of other tissues and organs, high incidence of scrapies in these sheep. In addition, we have not seen real cartilaginous metaplasia in any of the examined sclera in our cases.

Though some investigators dispute the systemic nature of DSLD and the underlying cause of it (Schenkman *et al.*, 2010), they have not been able to propose an alternative pathogenesis and a more fitting histopathological description.

Pathogenesis

Before we discuss pathogenesis of DSLD a short introduction on the composition of tendons and ligaments is warranted. Tendons and ligaments are composed primarily of water (approximately 70%) with the remaining 30% dry matter consisting of collagen and noncollagenous matrix and cells (tenocytes, ligamentocytes, proteoglycans and glycoproteins) (Dowling *et al.*, 2000). Suspensory ligaments evolved originally from interosseus muscles. In the modern horses the composition of the SL is similar to that of tendons with the exception of containing variable amounts (2-11%) of bilaterally symmetrical muscular tissue (Sisson, 1975).

Fibrillar type I collagen forms the structural back bone of tendons, and the precise alignment of its fibrils is essential for normal mechanical function of the tendon. Those fibrils can be identified by electron microscopy. They are organized into fibers, bundles and fascicles at the light microscopic level. During embryonic development, collagen fibrils are secreted as discrete segments 10-30 μm long into extracytoplasmic spaces between tenocytes (tendon fibroblasts). The segments form fibrils and are assembled into fibers which are then incorporated into the developing extracellular matrix (Birk *et al*., 1989). Proteoglycans, most notably decorin, modulate the formation and final sizes of the fibrils in the extracellular matrix (Yoon and Halper, 2005).

Proteoglycans play a prominent role among different biochemical components involved in the correct assembly of the collagen fibrils whose proper organization is essential to normal functioning of tendons. Proteoglycans consist of two components, a core protein and large, often numerous complex carbohydrate chains (so called glycosaminoglycans) that are attached to the protein. These proteoglycan molecules regulate collagen fibril formation and organization during normal growth and development, and are essential during tendon and ligament healing after injury. Small proteoglycans, such as decorin, fibromodulin, and biglycan have been identified throughout the superficial digital flexor tendon, and regulate tenocyte function, collagen fibrillogenesis, and the spatial organization of fibers (Yoon and Halper, 2005). The effects of these proteoglycans directly influence tendon strength (Hedbom and Heinegård, 1993; Svensson *et al*., 1995; Gu and Wada, 1996; Dowling *et al*., 2000).

Our most recent data point to the presence of an abnormal form of decorin in DSLD-tendons. Glycosaminoglycan structure and monosaccharide composition of extracellular matrix extracted were determined with high performance liquid chromatography analysis of chondroitinase ABC-digested glycosaminoglycans. The testing revealed an increase in the total content of sulfated disaccharides (components of the complex carbohydrate chains), particularly due to enhanced sulfation at 6-position of N-acetyl galactosamine with a subsequent decrease in the ratio of 4-sulfation to 6-sulfation disaccharides in the abnormal form of decorin. This correlated well with monosaccharide analysis using gas chromatography/mass spectrometry showing a significantly increased ratio of glucuronic acid to iduronic acid in DSLD-affected samples. This indicates that most glucuronic acid, a building block of chondroitin sulfate, was not converted into iduronic acid, a building block of dermatan sulfate. In other words, the DSLD-affected decorin is rich in chondroitin sulfate, whereas normal decorin is rich in dermatan sulfate (Eklund *et al.*, 2000). Our results differ from preliminary data by Schenkman *et al.* (2010) which suggest that a deficiency in one of the enzymes degrading aggrecan (so called ADAMTS5) may lead to accumulation of chondroitin sulfate-substituted aggrecan in affected SLs. They attribute the enzyme deficiency to its local entrapment in SLs.

We have shown that the change in sulfation of decorin leads to alterations in distribution of immunostained decorin (Fig. 3), and in biological activity, such as diminished binding of transforming growth factor β1 (TGFβ1) to DSLD-affected decorin (Fig. 4), and increased expression of TGFβ1 in DSLD tissues (Fig. 5) (Kim *et al*., 2010). Further studies are necessary to determine whether the altered TGFβ1 binding and expression are active participants in the disease process in analogy to human Marfan syndrome.

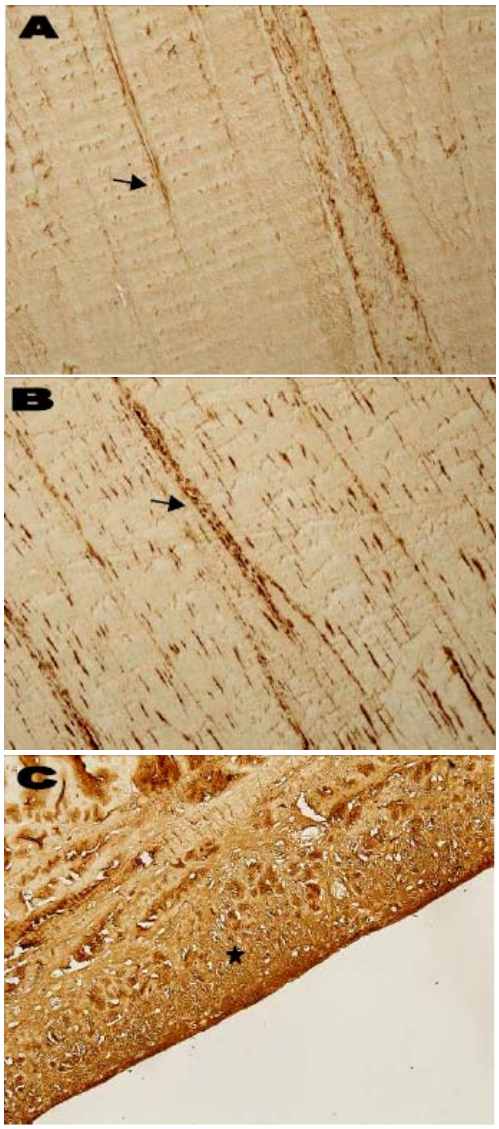

Fig. 3: Immunohistochemistry of superficial digital flexor tendon for decorin. Histological sections of superficial digital flexor tendons were immunostained with polyclonal rabbit LF122 antibody to decorin. Antigen–antibody complexes were detected with DAB staining. (A) Control tendon immunostained for decorin (→), original magnification X 200. (B) DSLD tendon, lightly infiltrated with proteoglycans, immunostained for decorin (→), original magnification X 200. (C) DSLD tendon with heavy accumulation of proteoglycans immunostained for decorin (*), original magnification X100. Immunostaining for decorin in control tendons is more evenly distributed, and with less intensity in the healthy tendon than in DSLD-affected tendon. Portions of this figure originally appeared in Kim *et al*. (2010).

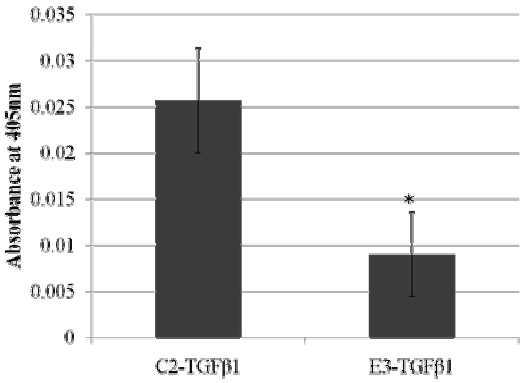

Fig. 4: ELISA measuring binding of decorin to TGFβ1. TGFβ1 (10 ng, in blocking buffer/Tween 20) was added to replicate wells coated with decorin (100 ng). TGFβ1 bound to decorin was detected by polyclonal TGFβ1 antibody. The decrease in binding of TGFβ1 to ESPA decorin was statistically significant when compared to TGFβ1 biding to control decorin (*, n = 3, $p < 0.05$). This figure originally appeared in Kim *et al.* (2010).

Excessive activity of TGFβ1 was identified as the main factor responsible for cardiovascular problems experienced in patients with Marfan syndrome, a human hereditary systemic disease affecting connective tissues. However, the primary defect in Marfan syndrome is a defect of fibrillin-1 rather than of one of the proteoglycans with changes in TGFβ1 expression as a secondary phenomenon. Patients with Marfan suffer from multiple problems, such as lens ectopia, cardiovascular problems (dissecting aortic aneurysm, mitral valve prolapse), abdominal herniae, musculoskeletal problems (arachnodactyly, joint hypermobility, tall stature) (Tsipouras *et al.*, 1992; Robinson and Godfrey, 2000; Ng *et al*., 2004). The histopathological changes in the coronary arteries, aorta and sclerae and anecdotal evidence of ruptured aortic aneurysm in some DSLD horses (Halper *et al*., 2006) together with altered TGFβ1 expression suggest its role in the pathogenesis of DSLD.

Management, treatment and prognosis

Degenerative suspensory ligament desmitis is a progressively debilitating disease that most often results in affected horses being retired from their current athletic career (Gibson and Steel, 2002). Reported treatments for DSLD-affected horses are largely empirical and directed at minimizing musculoskeletal pain and providing support for the suspensory apparatus.

Exercise should be restricted to a small paddock or large stall with secure, but not excessively deep footing that would excessively stress the supporting structures of the distal limb. Supportive half-limb bandages may provide temporary support and relief, however, must be changed or reset frequently (q 12-24 hrs). More recent work (Xie *et al.*, 2010) suggests that horses demonstrating mild to moderate signs of DSLD may actually benefit from moderate, controlled exercise. In this study, 4 and 8 weeks of controlled exercise did not exacerbate, and actually appeared to improve the clinical signs and lameness associated with DSLD in Paso Fino and Peruvian Paso horses as it related to lameness, suspensory cross-sectional area, and suspensory branch fiber pattern. Clearly, the effect of exercise on the progression of DSLD requires further investigation.

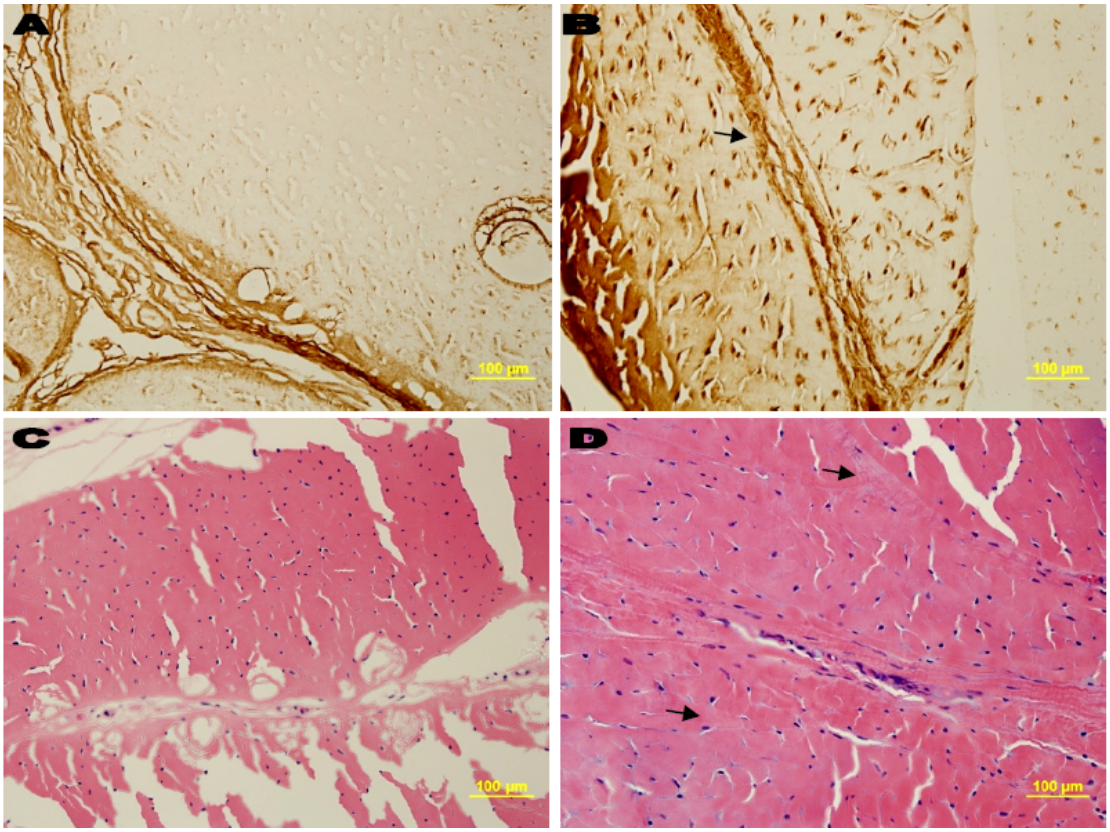

Fig. 5: Immunohistochemistry for TGFβ1. Histological sections of suspensory ligament were immunostained with antibody to TGFβ1. (A) Immunostained section of suspensory ligament from a control horse. (B) Immunostained section of suspensory ligament from a DSLD horse (→). (C) Hematoxylin and eosin-stained section of control suspensory ligament. (D) Hematoxylin and eosin-stained section of DSLD suspensory ligament lightly infiltrated with proteoglycans (→). This figure originally appeared in Kim *et al.* (2010).

Nonsteroidal anti-inflammatory drugs [phenylbutazone (2.2 mg/kg, q 12-24 hrs) or firocoxib (Equiox®, Merial Ltd, Duluth, GA USA, 0.1 mg/kg, q 24 hrs)] may be administered intravenously or orally to provide pain relief. They should not be administered subcutaneously or intramuscularly because they are too irritating and will cause an abscess or severe cellulitis. Topical application of 1% diclofenac cream (Surpass®, Boehringer Ingelheim, Germany) to the affected ligaments may also provide temporary pain relief without the risk of the systemic adverse effects associated with prolonged NSAID administration.

Application of egg bar shoes that extend 2-3 cm beyond the heel bulbs will help support the fetlock by moving the relative center of support forward (Young, 1993) and often improves the angle of the fetlock. This measure often results in rapid to immediate pain relief.

Despite diligent adherence to exercise recommendations, analgesic therapy, and corrective and supportive shoeing techniques, the clinical course of DSLD is most often progressive, debilitating, and career ending. The end result is all too often humane euthanasia due to persistent pain and the associated severe lameness.

Conclusions

DLSD is a debilitating, most likely of hereditary nature, equine disorder affecting tendons, ligaments, and other structures with high content of connective tissues. Though latest data indicate that the primary defect lies in excessive accumulation of an abnormal decorin and other, yet to be identified, proteoglycans, we have neither a diagnostic biomarker nor effective treatment for this disease. Supportive measures, such restricted exercise, supportive half-limb bandages, and nonsteroidal anti-inflammatory drugs are often ineffective in the long run and are followed by euthanasia in such cases.

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