Equine osteoarthritis: a brief review of the disease and its causes

Angela E Schlueter and Michael W Orth*
Department of Animal Science, Michigan State University, 2209F Anthony Hall, East Lansing, MI 48824, USA
*Corresponding author: orthm@msu.edu

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Abstract
Degenerative joint diseases, such as osteoarthritis, adversely impact the health of the equine athlete as well as the economics of the equine industry. Our understanding of the aetiology of osteoarthritis, although not nearly exhaustive, has increased substantially in recent years. Molecules, including cytokines, inflammatory mediators, and metalloproteinases, have been identified and associated with the progression of joint disease. Several factors, including trauma to the joint, immobilization, conformation, shoeing, and ageing, have been linked with osteoarthritis. Our continued efforts into elucidating critical biological mediators and risk factors, coupled with better chondroprotective therapies and diagnostic tools, should facilitate our ability to maintain the skeletal health of the equine athlete.

Keywords: cytokines; metalloproteinases; joint disease; risk factors

Impact of osteoarthritis in the equine industry
The equine industry is a growing industry that encompasses diverse disciplines ranging from sport horse to work horse, and has a sizeable share in the US economy. The American Horse Council Foundation (Barents Group LLC, 1996) reported that there were 6.9 million horses in the USA in 1996; 725 000 horses were involved in racing, 1 974 000 in showing, 2 970 000 in recreation and 1 262 000 in other activities. In addition, the equine industry directly provided 338 500 full-time jobs. The report also determined that in 1996 the equine industry produced goods and services valued at $25.3 billion, and the total contribution to the US gross domestic product was $112.1 billion.

Lameness is a major cause of wastage in horses and adversely affects the horse industry because one of the main factors determining a horse’s value is soundness, especially in athletic horses. Jeffcott and Kold assessed the wastage in Thoroughbred racchorses from conception to 4 years of age, and determined that lameness was the most significant factor responsible for failure to race, outweighing respiratory problems, colic or limited racing ability. Their study also indicated that, among 140 Thoroughbred two-year-olds evaluated, only 34 (24%) did not show any signs of lameness. Similar results were found in a study determining the wastage of racehorses between 1982 and 1983. The greatest number of days lost to training was caused by lameness (68%); among 314 horses examined, 53% were lame at some period during the racing season.

Osteoarthritis (OA) is one of the most common causes of lameness, and is of particular concern in horses because their value is closely tied to their soundness. Lameness that results from OA is a major cause of poor performance and early retirement of equine athletes. A survey performed at a veterinary school found that 33% of all equine patients had intra-articular lesions related to OA. Tew and Hackett randomly evaluated 72 equine joints at necropsy and discovered that 35% of them had evidence of grossly visible cartilage damage. Not only is this degenerative disease found in domestic horses, but it also occurs naturally in the joints of wild horses. Despite the huge economic importance of joint disease and OA in horses, our understanding of the pathophysiological mechanisms involved in joint degeneration in this species is limited. Whether OA is a single disease or is caused by several disorders with a similar final common pathway remains unclear.

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Aetiology of OA

OA, often referred to as degenerative joint disease (DJD) in the horse, is characterized by deterioration of articular cartilage, accompanied by changes in the bone and soft tissues of the joint. The end stage of OA results in a net loss of articular cartilage, causing pain, deformity, loss of motion, and decreased function. Horses have naturally occurring OA, which is similar to that of humans, and are often used as models to investigate the pathogenesis and treatment of OA.

Synovial joints are the joints usually associated with lameness in the horse. These joints have two major functions: to enable movement and to transfer load. Synovial joints consist of the articulating surfaces of bone, covered by articular cartilage, secured by a joint capsule and ligaments, and have a cavity containing synovial fluid. Articular cartilage is an avascular tissue, which serves as a shock absorber for bone and has a frictionless surface bathed in synovial fluid. This tissue consists of sparsely scattered chondrocytes (cartilage cells). The extracellular matrix (ECM) provides cartilage with its compressive strength and is primarily composed of type II collagen and proteoglycans (PGs). Collagen forms a fibrous network giving cartilage its tensile strength. Large aggregating PGs (aggregans), composed of a protein core with several glycosaminoglycan (GAG) side-chains attached to it, hydrate the collagen network and provide the tissue with viscoelastic properties and the ability to resist mechanical compression. When the joint capsule is disrupted, proteolytic enzymes are secreted into the synovial fluid and can facilitate PG and collagen degradation. In an attempt to repair structural changes in the ECM, chondrocytes proliferate and stimulate synthesis of these components. However, over time, the metabolic activity of chondrocytes shifts towards the breakdown of matrix constituents outshades new matrix synthesis, beginning the state where the breakdown of matrix constituents outshades new matrix synthesis. Articular cartilage covering sites of subchondral bone sclerosis is predisposed to the development of OA.

Soft tissues of the joint include the intra-articular ligaments, joint capsule, menisci and synovial membrane. Damage to intra-articular ligaments, which provide support for the joints and distribute normal surface stresses, can stimulate an inflammatory response and change the loading characteristics of the joint surface. An example of this phenomenon is shown by mechanical instability of the joint after transection of the cranial cruciate ligament. This surgical procedure produces joint laxity, loss of joint congruency, and abnormal cartilage weight-bearing forces and trauma that can directly and indirectly induce abnormal cartilage wear. Degenerative joint disease often develops in humans following meniscal injury. Increased stress across the knee joint induced by performing surgical meniscectomy stimulates OA in humans, rabbits and guinea pigs.

Chronic disease of the equine joint capsule, capsulitis, can lead to the formation of scar tissue and increased stiffness, leading to instability of the joint by changing its surface stresses. Acute synovitis and capsulitis may cause significant clinical compromise of the joint, and also contribute to the degenerative process by the release of cytokines, inflammatory mediators and enzymes. While the cause of acute primary synovitis has never been determined, the development of an acutely inflamed joint is prevalent in trained thoroughbreds and standardbreds.

Molecules associated with OA

Cytokines

Interleukin (IL)-1 induces and augments the pathological processes involved in inflammatory joint disease. Morris et al. were the first to identify IL-1 in the equine osteoarthritic joint, and found that equine IL-1 has many of the characteristics of IL-1 isolated from other species. IL-1 stimulates chondrocytes and synovial cells to release enhanced amounts of prostaglandin E2 (PGE2), PGs and matrix metalloproteinases (MMPs) such as collagenases and stromelysin, and increases nitric oxide (NO) production. Stimulation by IL-1 creates an inflammatory response that is similar to naturally occurring OA. As a result, IL-1 is often used to stimulate an inflammatory response in chondrocytes.

Equine explants stimulated with IL-1 have demonstrated an increase in the release of GAGs from the ECM. Decreased PG synthesis and increased MMP-3 activity have been reported in equine explants following stimulation with IL-1, while recombinant human interleukin-1β (rhIL-1β) induces the expression of MMP-13 in equine chondrocytes in monolayer culture and explants. IL-1 also induces IL-6.
synthesis in human cartilage from normal controls, patients with OA and patients with rheumatoid arthritis. Increased PGE2 and IL-6 concentrations were found in the synovial fluid of equine joints injected with IL-1β. In a subsequent study by Simmons et al. in which rhIL-1β was injected into the metacarpophalangeal (MCP) joints of horses, an increased concentration of IL-6 was also found. Other interleukins, such as IL-6, -8, -10 and -18, have been studied in arthritic cartilage as well, although the link to OA is not as clear for these cytokines as it is with IL-1.

Tumour necrosis factor-β (TNF-α) exerts many of the same catabolic effects as IL-1 since it activates similar cell signalling pathways. As an example, like IL-1 it upregulates both MMP-13 and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motif) enzymes. In equine chondrocytes, it greatly increased the gene expression of MMP-1, -3 and -13 while only mildly increasing the expression of tissue inhibitor of MMP-1 (TIMP-1). Models of inflammation in horses demonstrate an increase in TNF-α. However, TNF-α concentrations in synovial fluid are not considered reliable indicators of the severity of joint damage in horses.

**PGE2 and NO**

Prostaglandins are widely distributed in the body and mediate or modulate a variety of physiological and pathophysiological processes in many organ systems and tissues, including the haematopoietic, cardiovascular and reproductive systems. They are believed to bind to receptors on the sensory nerve endings, promoting the discharge of impulses and consequently causing an increase in pain.

Prostaglandins (primarily E group) are produced in inflamed joints and can cause a decrease in the PG content of the cartilage matrix. Actions of PGE2 in joints include vasodilatation, enhancement of pain perception, degradation of PGs and inhibition of PG synthesis from cartilage, bone demineralization and promotion of plasminogen activator secretion. Cyclooxygenase-2 (COX-2) is one of the rate-limiting enzymes responsible for the production of PGE2 from cell membrane phospholipids. IL-1 stimulates the synthesis of PGE2, and increased concentrations of PGE2 in affected joints suggest a causal link of this inflammatory mediator to the pathophysiological events of OA. Equine synovial cells and chondrocytes increased PGE2 production after stimulation with recombinant equine interleukin-1β (reIL-1β) and lipopolysaccharide (LPS). Exposure of equine synovial explants to reIL-1β enhanced expression of COX-2.

In addition, equine articular cartilage explants incubated with LPS or IL-1 had an increase of PGE2 released into the culture medium. Significantly higher PGE2 production has been reported in the medium of explants originating from horses with moderate OA, compared with normal joints. The PGE2 content in the synovial fluid of equine osteoarthritic joints was increased relative to levels in asymptomatic joints. The generation of specific COX-2 inhibitors for joint pain in humans demonstrates the significance of inhibiting PGE2 synthesis.

NO may also be involved in the pathogenesis of OA. This uncharged free radical is released from various tissues and cells, and is the product of a reaction between l-arginine and oxygen. NO has one unpaired electron and readily reacts with oxygen, superoxide radicals and transition metals, which may generate further destructive species. Stadler et al. first showed that articular chondrocytes have the ability to generate large amounts of NO. NO is a major component of the inflammatory response, and may mediate the suppression of cartilage matrix synthesis occurring in response to intra-articular cytokines. NO activates MMPs, suppresses PG synthesis and induces apoptosis in human articular chondrocytes. The death of chondrocytes from NO occurs under conditions where other reactive oxygen species are generated.

Although NO is generally thought to be an important mediator of the inflammatory response, it may have an anabolic function in inhibiting articular cartilage catabolism. NO inhibited degradation of aggrecan in equine explant cultures, suggesting that NO has an anticytotoxic role in PG degradation. However, the majority of research suggests that its overproduction has negative consequences in horses. Explant cultures of equine synovial membrane and articular cartilage released significantly higher amounts of NO when the explants originated from horses with OA. Simmons et al. injected rhIL-1β intra-articularly into the MCP joints of six horses, and measured nitric oxide synthase (NOS) in the synovial fluid of injected joints 6 h post treatment. Although the intensity and extent of inflammation were significantly greater in the IL-1β-exposed specimens compared with healthy specimens, no significant increase in the inducible isoform of NOS (iNOS) was found between the control joints and the joints exposed to IL-1. However, this might not be the case if different concentrations of IL-1 are tested. Increased NO synthesis occurs in chondrocytes and synoviocytes in response to LPS and IL-1 within a 48 h incubation period. In addition, LPS or IL-1 dramatically increased NO synthesis relative to non-stimulated controls in equine explants. An NOS inhibitor prevented cartilage degeneration in dogs with induced OA. Thus, inhibiting or minimizing NO production in the joints of horses would probably be beneficial.

**Metalloproteinases**

Although all classes of proteinases may be involved in the degeneration of the ECM, the MMPs may play the
pivotal role in cartilage destruction. These enzymes are characterized by a requirement for Zn\(^{2+}\) in their active site. Calcium is also required for the expression of full activity but does not reside in the active site. Overall, the MMPs are capable of degrading ECM components such as collagen, aggrecan, link protein and cartilage oligomeric protein\(^{62}\). This growing family of proteolytic enzymes has been divided into four main classes: collagensases (MMP-1, -8 and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3 and -10) and membrane-type (MMP-14, -15 and -17). MMPs are inhibited by a group of endogenously produced tissue inhibitors called TIMPs.

MMP activity increases in equine osteoarthritic joints\(^{63}\). Specifically, MMP-2 and MMP-9 have been found in synovial fluid from diseased equine joints\(^{40,64,65}\). The activity of both of these MMPs was upregulated in normal equine cartilage and synovial fluid following stimulation with IL-1\(\beta\)\(^{40}\). In fact, MMP-9 in synovial fluid could potentially be an indicator of joint damage\(^{40}\). Stimulation of cartilage explants with IL-1 also induced the synthesis of MMP-3 in young and adult horses\(^{43}\). rhIL-1 and LPS stimulated MMP-13 expression in equine chondrocytes and cartilage explants\(^{54,67}\). An exciting area of research is the development of assays to quantify the protein fragments of type II collagen degradation by MMPs such as MMP-13 in biological fluids\(^{68,69}\).

**Causes of OA**

Cartilage damage due to trauma, impact injuries, abnormal joint loading, excessive wear or as part of an ageing process can lead to changes in the composition, structure and material properties of the tissue\(^{30,70,71}\). These changes can compromise cartilage function in the strenuous mechanical environment normally found in weight-bearing joints. Regardless of the specific cause, the initial injury is usually mechanical in nature, with an imbalance between the load applied and the tissues' capacity to withstand that load\(^{72}\). Trauma to the joint, immobilization of the joint, poor conformation, improper shoeing and age are often preliminary factors that contribute to the onset of OA in the horse.

**Trauma**

Trauma to the joint is believed to be the primary cause of OA in the horse. Mackay-Smith\(^{3}\) referred to use-trauma, or trauma occurring from normal use of the joint, as a percursor factor of OA. Very strenuous exercise injures articular cartilage by increasing fibrillation of the cartilage and reducing PG content and quality. Cartilage no longer responds with improved biomechanical properties, and overload results from such factors as extensive and intensive exercise, fatigue, speed, and poor conformation or footing\(^{75}\). For example, a racehorse's pace generates millions of foot-pounds of force per mile, and the wear and tear produced on the joints during a race can be severe\(^{5}\). Also, in a rabbit trauma-induced model for studying OA, regular exercise accelerated subchondral bone thickening and cartilage damage after injury\(^{75}\). This could be a quite relevant model for the equine athlete.

Most lameness occurs in the forelimbs, because they carry 60–65% of the horse's weight and are subjected to higher load rates than the hind limbs\(^{74–76}\). The hind limbs propel the horse, while the forelimbs receive the shock of landing. However, this may vary among breed and performance event. Different areas of joints and joint surfaces in both the forelimb and hind limb are subjected to different types of loading, such as low-level constant loading during weight-bearing, intermittent loading during locomotion, and very high and sudden loading during training or racing\(^{77}\). The carpal, fetlock, proximal interphalangeal and distal intertarsal/tarsometatarsal joints are most frequently affected by OA.

The fetlock joint of the foreleg has the largest number of unique degenerative and traumatic lesions of any limb joint in racing horses\(^{78}\). Braman et al.\(^{79}\) topographically mapped contact areas and pressure distributions on the proximal articular surface (PAS) of the proximal phalanx (P1) under various clinically relevant loading conditions in the forelimbs of 13 horses. These authors found that certain areas of the PAS of the P1 are permanently loaded in the standing horse, and as the load was increased to mimic the walk or trot, the contact area enlarged in the dorsal, dorsolateral and dorsomedial directions. The joint pressures in the continuously loaded central area of the equine fetlock joint are relatively low in the standing horse, but may increase up to six-fold when loads are applied that can be expected during athletic performance.

Articular cartilage degeneration of the dorsal joint margins of the carpal bones in racehorses may be the direct result of trauma\(^{78}\). Repetitive exercise may induce the replacement of normal subchondral bone by sclerotic bone, therefore contributing to the pathogenesis of OA. Research into the effects of exercise on PG metabolism in the carpal joints has produced conflicting results. Palmer et al.\(^{80}\) assessed the relevance of site and the influence of exercise on articular cartilage PG synthesis and metabolism on third carpal articular cartilage in 16 horses. PG synthesis was increased in exercised horses relative to non-exercised horses at the end of a 6-week period. However, the increase in newly synthesized PG was not reflected in endogenous PG within the matrix at different sites on the third carpal bone. A significant correlation of site on endogenous PG was evident, with a greater concentration of PG located in the palmar aspect of the radial facet compared with the sites located on the dorsal aspect of the radial
facets or all sites on the intermediate facet. Total PG content on sites of the middle carpal joint increased in untrained Thoroughbreds with short-term exercise. PG content was greater at palmar sites overall, and dorsal sites of the high-intensity trained group had 12% higher PG compared with those of the low-intensity trained group. A contradictory study to those previously described evaluated the effect of strenuous versus moderate exercise on the metabolism of PGs in the articular cartilage from different weight-bearing regions in the equine third carpal bone. PG synthesis was reduced in both exercise groups and greater PG loss was found in the different joint regions of the strenuously trained animals. No change in PG size or ability to aggregate in different regions of any articular cartilage site was found in this study. The differences in the studies cited could be due to the use or non-use of sedentary controls and different exercise programmes. For example, Palmer et al. trained horses for 6 weeks, Murray et al. for 19 weeks, and Little et al. for 25 weeks. The fact that the longest exercise programme had decreased PG synthesis may be significant.

Low-motion joints such as the proximal interphalangeal, distal intertarsal and tarsometatarsal are vulnerable to the development of OA because they have a relatively smaller area of joint surface that must sustain the same weight-bearing load for a relatively longer period of time during joint movement. Both ring-bone and bone spavin can produce crippling lameness in horses. Although the aetiology of ring-bone and bone spavin is undetermined, the cause could be trauma to the periarticular soft tissues including the joint capsule insertions and periosteum. Ring-bone is a term used to describe DJD of the proximal and distal interphalangeal joint. This disorder most commonly occurs in horses forced to make quick turns and abrupt stops, such as Western performance horses, polo ponies and jumpers. Ellis and Greenwood evaluated six cases of ring-bone in young Thoroughbreds ranging from the age of 3 months to 4 years. All cases except one had other pre-existing or concurrent bone disease, which could have subsequently placed abnormal weight on the interphalangeal joint resulting in DJD. Ring-bone was the most serious cause of wasting in Norwegian Döle horses over 30 years ago.

Bone spavin is the most common cause of hind-limb lameness of athletic horses, and involves the distal intertarsal, tarsometatarsal and occasionally the proximal intertarsal joints. This degenerative disorder has been found in a variety of breeds including Quarter Horses, Thoroughbreds, Standardbreds and Icelandic horses. Wyn-Jones and May treated 30 horses and ponies for lameness due to bone spavin, finding that 25 of the 30 horses were lame in both hind legs and that lameness varied from slight to severe. Twenty-three per cent of Icelandic horses evaluated radiographically (379 total) had signs of bone spavin, suggesting a predisposition to the disease.

**Immobilization**

Reduced loading or immobilization, due to lack of exercise, can lead to atrophy or degeneration of articular cartilage. While excessive forces may lead to articular cartilage loss, removal of all mechanical stimulation leads to atrophy. When cartilage is subjected to high-pressure loads, PGs are compressed and water is expressed from the cartilage. Cartilage then expands as it is rehydrated upon alleviation of pressure. Physiological loading and motion are therefore essential to maintain the normal nutrition and metabolism of articular cartilage provided by exchange with synovial fluid.

Although several immobilization studies have been conducted, few have been done on horses. An early study investigating changes in the metabolism of PGs in immobilized limbs of sheep showed a decrease in GAG content of the non-load-bearing joint. PGs isolated from the immobilized limb were smaller than those isolated from load-bearing joints. Instability of the MCP joint was performed surgically in six horses by transecting the collateral and lateral sesamoidean ligaments. This procedure induced OA in all horses, which resulted in lameness, increased joint circumference, decreased joint range of motion and increased new synthesis of PG production. Horses immobilized with fiberglass casts from the proximal portion of the metacarpus down to the hoof tended to have lower hexosamine concentrations in articular cartilage biopsied from their cast joints. The contralateral limbs of each horse served as a mobilized control, and the control articular cartilage tended to gain hexosamine during the 30-day trial. These researchers saw little change in GAG synthesis in the cast joints, while the largest significant change occurred in the control. Similar results have been found in the rabbit. Thus, contralateral limbs are unsuitable for controls in immobilization studies because of their biological response to increased weight-bearing. Palmer et al. found a lower concentration of newly synthesized PGs in non-exercised horses than in exercised horses. Exercised horses had a noticeable increase in the early PG peak of newly synthesized PGs, while this did not occur in the sites of the non-exercised group. Immobilization studies performed with canine and rabbit limbs have indicated a depletion of PGs, defective aggregation of PGs and accumulation of water in the tissue. These problems may be reversed after remobilization.

**Conformation**

Conformation is defined by the physical appearance and outline of a horse, which is dictated primarily
by bone and muscle structures. Certain conformational traits can predispose the horse to lameness. Conformation defects such as ‘calf knees’, ‘knocked knees’ (carpus valgus), ‘bowed knees’ (carpus varus) and ‘bench knees’ cause the animal to load its carpus abnormally, and OA can result. In the rear legs, horses that are extremely straight in angulation of the stifle and hock, or are obviously sickle- or cow-hocked, are predisposed to conformationally induced lameness. Certain breeds’ characteristic conformation magnifies their risk of developing OA. For example, Icelandic horses with sickle hocks had a prevalence of radiographic signs of bone spavin of 42%, which was significantly higher than that of horses with straight (20%) or normal (19%) conformation. In addition, the prevalence of bone spavin was 19% in horses with a light skeletal type, whereas lesions were identified in 23% of those with intermediate and in 24% of those with heavy skeletal type. A more recent study confirmed this finding, and indicated that the prevalence of radiographic signs of DJD in the distal tarsus of Icelandic horses increased in horses with a smaller tarsal angle. Upright pasterns, base-narrow front limbs and a rectangular-shaped P1 in the Norwegian Døle horse are conformation defects that contributed to the development of ring-bone. Quarter Horses can be prone to OA because they have a relatively large body mass, poor carpal conformation, small feet and short upright pasterns.

**Shoeing**

Since the hoof capsule is malleable, the manner in which it is trimmed and shod can have a marked effect on the performance and soundness of the equine athlete. The hoof of the horse must be balanced to absorb high-impact vibrations when it is exposed to the repetitive trauma incurred during performance events and normal use. Maximum energy dissipation depends on proper hoof preparation and shoeing. Good shoeing is an art and maintenance of the natural angle and balance of the hoof is critical.

Improper shoeing can change the limb configuration of the horse, resulting in a modification of the forces placed on the joint surfaces. Increased abnormal wear and loading on the joint surface due to improper shoeing can contribute to degeneration of articular cartilage. The typical long toe/low heel conformation commonly seen in Thoroughbred racehorses can accentuate hyperextension-type injuries in the fetlock and carpus and cause direct injury to the foot in the form of OA in the distal interphalangeal (DIP) joint.

Corrective trimming and shoeing alters the hoof shape or angle to affect stance or stride and breakover, in order to help the horse achieve a more normal movement. Altered foot orientation, which could result from trimming and shoeing, influences intra-articular pressure in the articular contact area of the DIP joint. When a hoof is being actively re-formed, the change in shape during one trimming may be dramatic. Types of shoes and shoeing devices can alter the traction of the hoof. For instance, sliding plates and wide web shoes are often used on reining horses. These types of shoe provide inadequate traction for the horse, and can result in strained tendons or sprained ligaments. Traction devices, such as toe grabs, heel calks and borium, can provide too much traction. Excess torque on the limb and joints resulting from using these devices can lead to strain or sprain and may contribute to the development of OA. Horses shod with hoof caulks had altered joint angles, which could change the forces placed on the joint surfaces or the soft tissue structures in the lower limb. A study evaluating the effects of shoeing horses with wedges (angle 3.7 and 5°) showed that an increased elevation of the heel delayed unloading of the heel and an increased elevation of the toe advanced unloading. These results suggest that the horse does not compensate for an acute foot imbalance by redistributing the load under the foot. Increased joint pressure has been implicated in the progression of OA. An in vitro study evaluating the intra-articular pressure in the DIP joint showed that elevating the heels by 5° significantly increased DIP pressure.

**Age**

Advancing age is the most significant risk factor for OA in humans. In horses, however, OA is known to develop in animals as young as 2 years of age. Young performance horses are most likely to develop OA early in life, because of the emphasis on racing and showing young horses in futurities and other events. Training horses at a young age may precipitate damage to joints unable to withstand the extreme forces they are subjected to during training and competition. Racing and training may accelerate the naturally occurring age-related changes. In addition, some horses may be genetically predisposed to developing OA due to either age or training, while other horses may never be prone to the disease.

Pathological and arthroscopic examinations have shown that OA is commonly observed in the joints of older horses and in specific locations within a joint. Naturally occurring OA also becomes more severe with age in untrained wild horses. Increased severity of lesions is correlated with subchondral bone sclerosis and ossicles with increasing age. Age is also a significant cause for the prevalence of OA in Icelandic horses. Many studies have described surgical treatment of horses diagnosed with OA ranging from the age of 1 year up to the age of 21.
Similar to humans, as the horse ages, the biochemical properties of articular cartilage change. Several recent studies have investigated the effect of age on the biochemical characteristics of equine articular cartilage. Variations in biochemical characteristics of cartilage in relation to site and age showed no significant change in cartilage collagen between horses ranging from 4 to 30 years old, but indicated that non-enzymatic cross-linking was higher in older horses and was linearly related to age\textsuperscript{106}. A steady increase in pentosidine cross-linking increased with age from 5 years onward, resulting in a 10-fold increase up to the age of 30 years. Cross-linking of articular cartilage by non-enzymatic glycation is expected to result in stiffer, more brittle tissue that is more vulnerable to damage by mechanical loading. Non-enzymatic cross-linking during ageing may predispose older horses to development of OA.

The biochemical characteristics of articular cartilage in mature cartilage differ from those of immature cartilage at different sites on the joint surface. No significant differences in water content and hydroxylsylpyridinoline cross-links were found at two different sites of the MCP joint in neonatal, 5-month-old and 1-year-old horses. However, differences in DNA, GAG, collagen and hydroxylsine content between sites paralleled those shown in the mature horse\textsuperscript{106}. In a more recent study, the same researchers investigated the influences of age and exercise on the biochemical characteristics of articular cartilage\textsuperscript{107}. Neonatal foals showed no site-specific biochemical heterogeneity, in contrast to mature horses. The process of formation of site differences was almost completed in exercised foals at age 5 months, but was delayed in those deprived of exercise. They concluded that the functional adaptation of articular cartilage to mechanical loading occurs during the first 5 months postpartum, and that a certain amount of exercise is required to sustain this adaptation. Joints of horses less than 2 years of age had significantly higher cell numbers, total collagen and DNA content, and lower PG content, relative to mature horses ranging in age from 2 to 20 years old\textsuperscript{108}. No significant difference in these measurements was found within the mature age groups. Another study has reported no significant difference in collagen or GAG content in cartilage derived from horses aged 2–5 years\textsuperscript{109}. Chondroitin sulphate (CS), the most abundant GAG in aggrecan, and keratan sulphate (KS), the most widely distributed GAG in aggrecan, have both been reported to change with age. The sulphation patterns in CS chains affect the specific properties and functions of these molecules. Cartilage degeneration in the MCP joints of racehorses was accompanied by deposition of CS chains with altered sulphation patterns\textsuperscript{110}. Six-sulphation of internal and terminal CS residues increased with age. The same phenomenon has been reported in human studies\textsuperscript{111}.

High KS concentrations were reported in foals from 1 week after birth to 3 months of age\textsuperscript{112}. These values decreased rapidly from 3 to 5 months, and gradually reached adult values between the ages of 5 and 18 months. This pattern also has been reported in children\textsuperscript{113} and puppies\textsuperscript{114}. Todhunter \textit{et al}.\textsuperscript{115} had a similar finding, and reported a significant relationship between age of foals and plasma KS concentration. Mean plasma KS concentration peaked when foals were 10 weeks old. Age affected KS concentration in the synovial fluid of 32 clinically normal horses. However, no significant effect of age on plasma KS concentration was seen in normal adult horses with a mean age of 65 months. An earlier study also reported no age-related changes in synovial fluid KS concentrations in mature horses ranging in age from 8 to 30 years old\textsuperscript{116}.

Based on explant studies, ageing equine cartilage is not as sensitive to stimulation of PG synthesis by link peptide\textsuperscript{117}. In humans, the concentration of osteogenic protein-1, a growth factor found in cartilage, decreases dramatically with age\textsuperscript{118}. Thus, although some gross measurements might stay relatively constant, subtle changes in the metabolism of chondrocytes over time may facilitate degenerative changes.

\textbf{Conclusion}

The focus of this brief review was to provide updated information concerning equine OA and factors associated with it. Exercise is essential to the horse’s wellbeing. Although we do not know unequivocally how to prevent OA, our molecular understanding of it and how to monitor it are improving quickly. In the near future, intensive research efforts should identify better markers for monitoring cartilage loss and provide more information regarding how chondrocytes adapt to stress and ageing. Using relatively non-invasive measures to monitor the effects of training regimes and management on joint health should facilitate the care of the equine athlete. This strategy is currently being used to monitor bone health in horses under various conditions\textsuperscript{119–122}. Furthermore, chondroprotective nutraceuticals, diagnostic tools and therapeutic strategies will improve and expand.

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