Osteoarthritis (OA), also termed degenerative joint disease, is a major cause of lameness and a common problem in all types of horses and can affect a number of different joints. In racing and performance horses it often affects the high motion joints such as the carpal and fetlock joints, whereas in horses used for less strenuous activities it is more common in the low motion joints such as the distal tarsal and proximal interphalangeal joints.

In most instances OA develops in previously normal joints after injury of those joints. Injury may occur at any age, so that the predisposing causes of OA include: osteochondrosis, synovial inflammation due to trauma, infection or chemical irritation, joint instability subsequent to ligament or meniscal damage and fatigue failure of subchondral bone due to repetitive loading. The onset of structural changes and clinical signs may begin at any age after the primary insult. The rate of progression may range from slow to rapid, depending on the nature and severity of the initiating factor. The degenerative process is perpetuated by the release of cytokines and neurotransmitters from inflamed tissues, poor synovial perfusion due to increased joint pressures from effusion, and bone and cartilage fragmentation that cause both physical damage and synovial inflammation.

These processes result in synovial proliferation, periarticular new bone formation and articular cartilage degeneration. Articular cartilage in horses has limited healing potential and therefore its loss is irreversible. The loss of articular cartilage represents a culmination of failure of the articular cartilage to withstand the cyclic trauma of athletic activity and this may be complicated by aging changes. Pain may be due to synovial inflammation, joint capsule distension, increased subchondral bone pressure and direct stimulation of subchondral bone pain receptors. Treatment regimes generally involve the control of pain and inflammation, rest and the protection and encouragement of chondrocyte anabolism. A multitude of treatment options for OA exist e.g. corticosteroids, classical non-steroidal anti-inflammatory drugs, disease-modifying agents and the nutraceuticals. The aim of therapy should be to reduce inflammation, neutralise cytokines and enzymes and encourage synthesis of cartilage components, without any detrimental effect on the cartilage.

Anatomy
Microscopically, hyaline articular cartilage is composed of water (approximately 75%), type II collagen (approximately 15%), proteoglycans (approximately 10%) and chondrocytes (only 2%). Proteoglycans, which consist of a large number of highly negatively charged polysulphated glycosaminoglycans, are responsible for drawing water molecules into the extracellular matrix and providing compressive stiffness. Likewise, the anatomical arrangement of collagen fibrils at various depths of cartilage provides structural support, which accounts for tensile stiffness. The collagen fibrils and their arrangement also limit water content within the cartilage. Together, proteoglycans and collagen fibrils are mainly responsible for the resiliency of hyaline cartilage and its inherent biomechanical properties.

The subchondral bone beneath the hyaline articular cartilage most likely has significant effects on the cartilage above it. The subchondral plate is thinner than cortical bone in other sites in the body, and its stiffness modifies the compressive forces to which articular cartilage is subjected. The blood supply within the subchondral bone is important in cartilage nutrition and the cells within the subchondral bone may secrete peptides that...
regulate chondrocyte function. Additionally, its properties, such as blood supply and cell content, may have important implications on nutrition and peptide regulation of chondrocyte function. The synovial membrane is a vascular connective tissue that lines the inner surface of the joint capsule and articulates with itself or articular cartilage. The microvasculature within the synovium is responsible for generating synovial fluid, an admixture of a protein-rich filtrate of blood and synoviocyte-derived hyaluronic acid (HA). Synovial capillaries have fenestrations that contain small pores covered by a thin membrane. This anatomical feature acts as a biological sieve on various small molecules that gain access to the synovial fluid. Synoviocytes are a unique feature of the membrane and their functions vary. These functions include phagocytosis and synthesis of hyaluronate as well as synthesis of low molecular weight mediators such as interleukin-1 (IL-1), prostaglandins, and proteases, all of which have important affects on cartilage.

The synovial fluid is a dialysate of plasma with important proteins such as HA and lubricin added to it. HA and lubricin seem to provide the synovial fluid with its unique properties of boundary lubrication and steric hindrance. The properties of steric hindrance obstructs solute passage through the fluid surrounding the HA molecules. This is important in reducing the interaction of enzymes, antigens or cytokines with target cells.

Pathways of osteoarthritis
Joint injuries arise as a consequence of physical disruption of tissues due to mechanical stress. This may occur due to (1) abnormal forces on normal cartilage or (2) forces on abnormal (diseased) cartilage. Most commonly affected joints are the carpi, fetlocks and distal hock joints.

Abnormal loads on a normal joint:
Supraphysiological strains may arise as a consequence of an accident, such as a fall or collision, and may result in gross disruption of articular tissues including chondral/osteochondral fracture, partial or complete erosion of articular cartilage and ligament or capsule tears. A more frequent cause of joint injury in horses is fatigue damage of osteochondral tissues through repetitive loading, particularly at high speed. Both cartilage and bone are viscoelastic materials, i.e. their mechanical properties vary with the rate of loading, and both become more brittle (prone to fracture) with high strain rates. Consequently, impact loads are much more damaging to joint tissues than loads of similar magnitude applied in a more gentle fashion. Repetitive high-speed exercise resulting in cyclical impact loading of a joint is most likely to result in maximum injury.

There are also reparative mechanisms that take days or weeks to complete. Repeated impact loading on a daily basis is more likely to overwhelm such mechanisms, leading to cumulative damage. Other factors likely to affect the rate of loading of the limbs, such as the surface of a track and shoeing, can also be expected to influence the incidence of joint injury.

Conditions that result in joint instability and/or loading in abnormal planes are a risk factor for joint injury. Conformational abnormalities, including poor foot balance, particularly in the mediolateral plane, are recognized as risk factors for joint disease in the distal limb of the horse. Ligamentous injuries are frequently associated with, and implicated in, the etiopathogenesis of osteochondral injuries of associated joints. Furthermore, the pattern of loading of the limbs, and hence joints, is altered by lameness and therefore, continued exercise of a lame horse may be considered a risk factor for joint injury.

Normal load on an abnormal joint:
Articular tissues compromised by existing disease are more prone to physical damage due to a structurally weakened matrix and/or impaired ability to initiate reparative processes due to cell death or dysfunction. Intra – articular infection, developmental joint abnormalities, iatrogenic toxic insult following intra – articular injection and prolonged periods of immobilisation of a joint within a rigid cast have all been implicated as causes of joint disease. Inappropriate levels of exercise during the recovery phase from these diseases
will significantly increase the risk of joint injury. The joints that are usually affected are the distal joints of the legs because they are the major shock absorbers. In the forelimb, it is usually the carpus and fetlock. In the hind limb it is commonly the distal tarsal joints.

Up-regulation of catabolic processes is a fundamental aspect of cartilage injury and disease. Chondrocytes and synoviocytes are a rich source of inflammatory mediators and enzymes capable of degrading the extracellular matrix. Under physiological conditions, chondrocytes regulate a dynamic metabolic steady state in which anabolic and catabolic processes are balanced; there is a steady turnover of molecules, which is essential for maintenance of a healthy matrix. Regulation of enzyme activity is at 3 different levels.

Synthesis/secretion of proteinases is altered by inflammatory mediators, principally the cytokines interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α). Enzymes are secreted as latent proenzymes and have to be activated extracellularly. Enzyme activity is modulated by tissue inhibitors of metalloproteinases (TIMPS), which are produced by a variety of cell types, including chondrocytes and synoviocytes. Following joint injury there is up-regulation of synthesis of IL-1 and TNF-α, increased synthesis of enzymes and exhaustion of TIMPS.

Loss of articular cartilage is the major cause of joint dysfunction and disability in joint disease. Severe trauma may cause gross disruption of the joint surface with complete erosion of cartilage and possible involvement of subchondral bone. Subchondral bone is an integral component of the synovial joint; it supports the articular cartilage, maintains shape of the bearing surface and transmits loads from the joint to the rest of the bone. It is well established that subchondral bone is an important focus of pathology in long-standing joint disease (hence the term ‘osteoarthritis’) and changes to this region are often identified radiographically as a characteristic feature of joint abnormalities in the horse.

**Clinical signs**

Synovitis is common as a primary condition in athletic horses and is frequently the precursor of more widespread and chronic joint disease. Irritation through repeated mechanical trauma is presumed to be the major cause of synovitis, which is reflected in the observation that high-motion joints, such as the metacarpophalangeal, metatarsophalangeal and carpal joints, are most frequently affected. Synovitis may also arise secondarily to primary osteochondral injury, through the effects of inflammatory mediators, cartilage wear fragments or free proteoglycans within synovial fluid. Infection and intra-articular injection are well-recognised causes of synovitis. With chronic osteoarthritis, joint mobility is reduced but there may not be pain on flexion of the joint. There may be lameness that has gradually worsened over time or lameness, which improves with exercise, i.e. the horse ‘warms up’. In cases where there are multiple joint involvements, the horse may appear generally stiff at one or all gaits. In an older horse, the main sign of abnormality may be difficulty in standing up after a period of lying down.

**Principles of therapy**

It is important to understand that there is no cure for OA and that all of the therapy is aimed at slowing the progression of the disease and alleviating the clinical signs. The aims of all therapeutic procedures are to prevent the progressive loss of articular cartilage. Many instances of early joint disease mainly manifest as synovitis and capsulitis and their appropriate treatment will delay or prevent the cartilage loss of OA. On the other hand, timely and appropriate surgery for intra-articular fractures, osteochondritis dissecans (OCD) and other traumatic injuries to joints is also a necessary part of preventing OA. The chosen treatment will depend on the severity of the disease and the amount of work the horse is expected to perform.

**Non-steroidal anti-inflammatory drugs (NSAID’s)**

NSAIDs are the most commonly prescribed drugs for the treatment of pain and inflammation in humans and the same is probably true in the horse.

The principal action of most NSAID’s is the inhibition of cyclooxygenase (COX), the
first in a series of enzymes responsible for the conversion of arachidonic acid to prostaglandins. There are two forms of COX, the first that produces physiologic levels of prostaglandins in a constitutive manner (COX 1), and an inducible form of the enzyme (COX 2) which is responsible for the elevated levels of prostaglandins observed during inflammatory events in a variety of tissues. It appears that the activity of COX 1 is responsible for many of the homeostatic properties ascribed to prostaglandins and toxicity is predominately related to sustained COX 1 inhibition. Most currently available NSAID’s inhibit the activities of both COX isoforms, however the proportion of inhibition of COX 1 vs. COX 2 varies among compounds.

In addition to COX inhibition, NSAID’s have other anti-inflammatory effects. For example, carprofen reduces oedema and joint effusion in experimental joint disease models in horses by a non-COX mediated pathway and it has been reported that ketoprofen inhibits both lipoxygenase and COX. Moreover, at least some NSAID’s are capable of inhibiting elements of cellular inflammation. Thus, it is clear that a number of NSAID’s possess anti-inflammatory actions other than COX inhibition.

At present, phenylbutazone is the most popular and economical agent used in horses, and its clinical efficacy appears to compare favourably with other NSAID’s. The clearance of phenylbutazone from acidic (inflamed) tissues is slower than plasma elimination, indicating that therapeutic effects of phenylbutazone may persist in tissues after plasma levels have decreased to negligible levels. As prostaglandins are not the sole mediators of the pathophysiologic events and attendant pain in inflammatory processes, it is understandable that NSAID’s have certain limitations with respect to their analgesic and anti-inflammatory potency.

Pain relief from NSAID’s is mainly, but not exclusively, related to COX inhibition. It should be noted that prostaglandins themselves do not produce pain, except when present in large quantities. Thus, NSAIDs’ main actions occur at sites of inflammation, where they reduce the concentrations of PGE_2. Prostaglandin E_2 is known to sensitize nerve endings to mechanical stimuli and amplify the chemical activation of pain receptors by other inflammatory mediators such as bradykinin and histamine, both of which act to lower the pain threshold. Because NSAIDs’ principal action is to reduce the “hypersensitizing” effects of prostaglandins in inflamed tissues, they are poor analgesics for noxious stimuli applied to normal tissues compared to narcotics and local anaesthetics.

Experimental work investigating the phenylbutazone safety margin suggests doses that do not exceed 2.2 mg/kg or less twice a day are relatively safe. The margin of safety is drastically reduced if this dose is exceeded. Obtaining an accurate weight using conventional methods such as a weight tape, body score system or scale is of utmost importance when calculating the amount to be administered.

Intra-articular corticosteroids

Their use in horses and people remains highly controversial due to what some would state as “emotion-laden criticism”. The emerging stand by many clinicians seems to be that intra-articular steroid effects can be extremely beneficial when used judiciously. Undoubtedly, detrimental effects on cartilage can occur and are contingent on:

- type of corticosteroid used,
- concentration,
- duration of exposure, and
- many other cell and tissue variables.

Corticosteroids (CSs) bind to cell receptors (CSRs), which go to the cell nucleus and modulate expression of target genes. Corticosteroids potently inhibit a protein called NF-jB by increasing a protein that specifically blocks NF-jB. Since NF-jB is integral for enhancing inflammatory cytokine production, inhibiting this molecule drastically decreases inflammation. CSRs are present in neutrophils, lymphocytes, monocytes and eosinophils and possibly mediate all corticosteroid effects. Specifically, neutrophil function and, to a lesser degree, movement are effected by CSs. Lysosomal enzymes and neutrophilic
phagocytosis can be negatively affected by higher doses of CSs but more physiological steroid doses may not inflict as negative a response on the cellular immune system.

Inhibiting prostaglandin production may be the most recognized influence of CSs on inflammation. This action takes place at the beginning of the inflammatory cascade that inhibits phospholipase A₂ (PLA₂) via the steroid-inducible group of proteins called lipocortin. These proteins inhibit phospholipid hydrolysis by PLA₂, which prevents membrane phospholipids from mobilizing arachidonic acid. By inhibiting PLA₂, fatty acids, such as arachidonic acid, can no longer be oxygenated by cyclooxygenase and lipoxygenase enzymes to form the eicosanoids. Certain CSs studies have shown stimulatory effects on glycosaminoglycans and DNA synthesis by chondrocyte culture when more “physiological” doses were used. Furthermore, using small doses of hydrocortisone in human osteoarthritic chondrocytes has also shown inhibition of metalloproteinase synthesis and proteoglycan catabolism. Conventional wisdom from recent literature certainly suggests beneficial effects of intra-articular CSs when used judiciously.

Methylprednisolone acetate (MPA): Beneficial effects of MPA include minimizing the transcription of harmful molecules such as Interleukin-1β, MMP13 (collagenase 3) and others that directly cause matrix degeneration. Harmful effects include chondrocyte necrosis, inhibition of proteoglycan core protein and procollagen synthesis. Dosage of MPA seems to predict the fine balance between inhibition of inflammation with overall beneficial effects on the joint or destruction of matrix and disruption of normal chondrocyte metabolism.

Betamethasone: Like MPA, betamethasone is considered an intermediate to long-acting CS. In a clinical study, betamethasone was administered into joints of exercising horses with osteochondral fragments. The dose was considered to be more physiological. No significant detrimental changes were noted in the cartilage 56 days following administration of betamethasone in both exercised and unexercised horses.

Triamcinolone: The results of an in vitro study indicate that triamcinolone can potentially inhibit many of the detrimental molecules that result from inflammation without negative effects on the transcription of extracellular matrix genes. In light of these findings, 6–12 mg of triamcinolone per joint should be an adequate dose for anti-inflammatory effects.

Combined use of HA and corticosteroids: There is some support of the combination of TA and HA being beneficial in one study of 16 human patients with knee osteoarthritis. This study entailed a one-year, single-blind, randomised protocol in which 24 patients were treated with intra-articular HA once weekly for 3 weeks and then again at 6 months (total of 6 injections) (Ozturk et al. 2006). Sixteen of these patients also had 1 ml of triamcinolone prior to the first and fourth HA injections. They were evaluated using the WOMAC index (used to assess patients with osteoarthritis of the hip or knee using 24 parameters including 5 indices of pain, 2 of stiffness, 7 of social function and 10 of emotional function) and found that the results were better with the combination of these 2 products. There was no progression of OA on MRI in either group. There is indirect evidence that the use of HA together with triamcinolone acetoneid could provide clinical benefit in the horse. In a recent study the use of intra-articular HA, as well as intra-articular Adequan was assessed in the CSU chip fragment model (Frisbie et al. 2009). Intra-articular injection of 20 mg of HA was done at 14, 21 and 28 days. There was significantly less cartilage fibrillation with HA at Day 70 despite less impressive reduction of synovial effusion and synovial membrane vascularity and subintimal fibrosis compared to Adequan (Frisbie et al. 2009). Combining a potent anti-inflammatory corticosteroid like betamethasone or triamcinolone with the chondroprotective HA could provide good results in the horse.

Corticosteroids and laminitis: Fear of laminitis has caused less use of CSs by some equine clinicians, despite scientific studies demonstrating its effectiveness as well as its chondroprotective properties. Anecdotal associations were made and maximum doses
established based on a report by Genovese in 1983 of no cases of laminitis in 1200 horses treated with triamcinolone when a dose did not exceed 18 mg. A more recent publication provides the first follow-up study with data on the potential for triamcinolone acetonide to produce laminitis and the conclusion was that there was no association between the occurrence of laminitis and the intra-articular use of triamcinolone (McCluskey and Kavenagh 2004). Review of the literature by two authors revealed that good evidence linking laminitis to corticosteroid injection was lacking and that a large-scale multicentre trial was needed (Bailey and Elliott 2007).

Steroid arthropathy: This condition was first reported in the human literature following intra-articular corticosteroid therapy (Salter et al., 1967; Moskowitz et al., 1970). Changes observed were loss of joint space, signs of instability, and osteonecrosis. Currently, this condition has a low incidence and may merely represent a normal or occasionally accelerated progression of OA rather than a direct effect of corticosteroid therapy (Trotter, 1996b). These views are shared by other clinicians worldwide who have evaluated tissues from horses with severe OA following repeated injections of CSs combined with continued exercise (Owen, 1980; Trotter, 1996).

Postinjection flare: This condition has been reported to have an incidence of as low as 2% (Hollander, 1970). It is usually self-limiting but is associated with some discomfort necessitating NSAID therapy. The nature of the inflammation is believed to be caused by the microcrystalline characteristics of different corticosteroid preparations, as well as the dose and particular ester that is administered intra-articularly (Trotter, 1996). With the advent of longer-acting, branched-chain esters, the incidence of postinjection flare has decreased; however, clinicians should note that flare has been reported after intra-articular injection of triamcinolone hexacetonide (Gordon and Schumacher, 1979; Berger and Yount, 1990; Trotter, 1996b).

Potential of infection: The potential for infection following corticosteroid or any other drug into a joint is of great concern for practitioners. While the incidence is low, the infections can be devastating to the patient and expensive to treat. In a study evaluating the clinical and synovial fluid effects of methylprednisolone acetate injection with concurrent Staphylococcus aureus arthritis infections in horses, a delayed appearance of symptoms occurred (Tulamo, 1989). Although the incidence of infection is low, strict asepsis should be followed with intra-articular injections and the combination with an antibiotic, like amikacin, is frequently practiced.

PLEASE FIND INSTRUCTIONS TO ANSWER CPD QUESTIONS ON WEBSITE ON PAGE 5

CPD Questions:

Question 1
Regarding articular cartilage damage, which of the following is considered the most prominent factor in the development of OA:

a) Increase in hyaluronic acid concentration in the cartilage matrix.
b) Increase in synovial fluid quantity.
c) Reorientation of the matrix collagen fibers.
d) Loss of proteoglycans in the cartilage matrix.
e) Decrease of Interleukin – 1 in the synovial fluid.

Question 2
Which one of the following will not perpetuate the degenerative process in OA:

a) Release of cytokines and neurotransmitters.
b) Poor synovial perfusion.
c) Synovial inflammation.
d) Decreased synovial fluid in the joint.
e) Bone and cartilage fragmentation.

Question 3
What is considered the hallmark of radiographic changes for OA:

a) Periarticular osteophyte formations.
b) Enthesiophyte formation.
c) Increase in joint space.
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d) Increase in soft tissue density surrounding the joint.
e) Subchondral bone sclerosis

Question 4
The main action of NSAID’s in osteoarthritis is:
a) Inhibiting PGE2 at the site of inflammation.
b) Inhibiting cycloxygenase and lipoxygenase.
c) Decreasing noxious stimuli in normal tissues.
d) Decreasing the amount of NF-jB in a joint.
e) Inhibiting cellular inflammation in the joint.

Question 5
The side effects of NSAID’s in osteoarthritis are drastically reduced when:
a) NSAID’s are fed with long stem hay.
b) The dosage does not exceed 5 mg/kg bid.
c) Anti-ulcer medication like Ulsanic is administered in conjunction with NSAID’s.
d) The dosage does not exceed 2,2 mg/kg bid or oid.
e) NSAID’s are fed with concentrates once daily.

Question 6
Steroid arthropathy is thought to be due to:
a) Injection of a long-acting corticosteroid.
b) Injection of too large a dose of corticosteroid.
c) Accelerated progression of osteoarthritis.
d) Iatrogenic infection.
e) Combining a long acting corticosteroid and HA.

Question 7
Corticosteroid receptors are present in all the following cell types except:
a) Neutrophils.
b) Basophils.
c) Monocytes.
d) Eosinophils.
e) Lymphocytes.

Question 8
Postinjection flare in OA is thought to be the result of:
a) Longer-acting, branched-chain corticosteroid esters.
b) Combining corticosteroids and HA in a joint.
c) Infection after administering a corticosteroid into a joint.
d) Administering PSGAG into a joint.
e) Microcrystalline characteristics of different corticosteroid preparations, as well as the dose and type of ester.

Question 9
In horses that perform at speed, OA is more common in the:
a) Distal tarsal joints.
b) Hind coffin joints.
c) Front fetlock joints.
d) Elbow joints.
e) Front pastern joints.

Question 10
Hyaline articular cartilage is composed of the following components except:
a) Water.
b) Type 1 collagen.
c) Proteoglycans.
d) Chondrocytes.
e) Glycoproteins.

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