Lameness

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Microstructural Alterations and Navicular Bone Degeneration

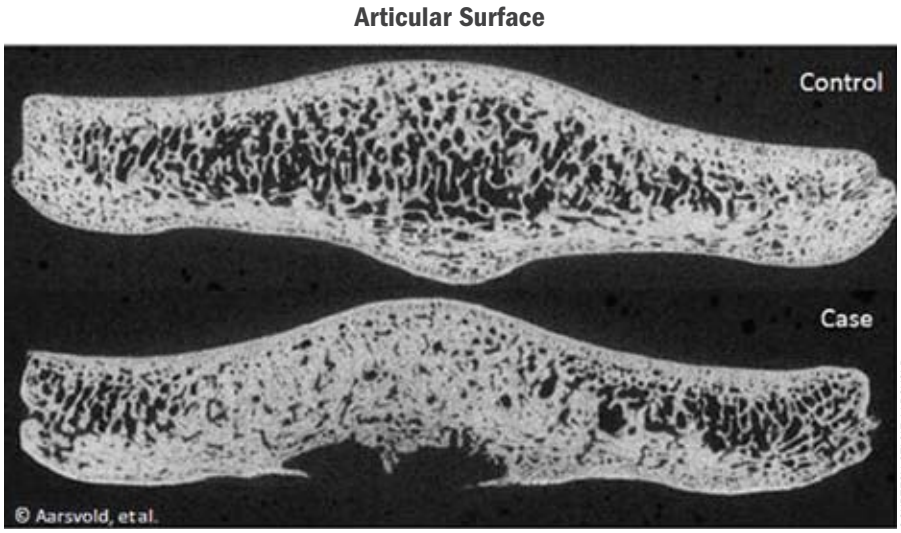
Veterinarians examine navicular disease cases using lameness exams and various imaging methods, but key to understanding this common debilitating disease and pinpointing treatment is knowing what's going on at the microscopic level. Recently, a team of researchers evaluated microstructural changes in diseased navicular bones as compared to healthy navicular bones. Stacie Aarsvold, BS, a fourth-year veterinary student at the University of California, Davis, presented the results.

"Navicular bone pathology (disease) is an important component of foot lameness in horses," Aarsvold said, adding that there are a number of common clinical radiographic findings related to the navicular bone including:

- Enlarged synovial invaginations ("holes" in the navicular bone that fill with synovial fluid, which is found in joints);
- Bone fragmentation;
- Enthesophytosis (small bone spurs that occur on the edges of the navicular bone);
- Flexor cortical lysis (decomposition of the outer tubular layer bone—the cortical bone—surface in contact with the deep digital flexor tendon); and
- Medullary sclerosis (increased density in the bone's medullary canal—the marrow cavity).

"However, the pathogenesis and interrelationships of these changes remain poorly understood," Aarsvold noted. "The primary objective of this study was to more fully characterize alterations in microstructure of severely diseased navicular bones."

Aarsvold et al. compared 13 diseased navicular bones *in vitro* (in the lab) with seven control (healthy) navicular bones using microcomputed tomography. The team evaluated the bones' trabecular (the scaffolding that gives bone its strength) quality, morphology (structure), porosity, mineral density, and cortical thickness.



COURTESY STACIE AARSVOLD

Researchers found that diseased navicular bones had a number of pathologic changes compared to controls including bone spurs, decomposition of the outer bone layer, and bone fragmentation.

The team found that "diseased bones had more and denser cortical bone; fewer, thicker, and less-organized trabeculae; and thicker articular (joint) and flexor cortices than control bones." Midline flexor cortical lucencies (areas of translucence) were found in both diseased and control bones; however, only the diseased bones had "flexor cortical surface disruption."

So, what does all this mean? Aarsvold explained that she and her colleagues saw microstructural changes in the compact and trabecular areas of these severely diseased bones that were similar to what is seen in bone modeling (laying down of new bone) and pathology in other types of diseased bone. She noted that these changes are evidence that the biomechanical environment of the entire bone has been altered on all layers.

"This study helps to clarify radiographic abnormalities identified in horses with navicular degeneration," she concluded. "We hope to apply this type of research to less severely affected bones in the future, which would allow us to get a better idea of the disease progression."

Humeral Stress Fracture Location: Effect on Racing Examined

A stress fracture is a stress fracture, regardless of its location, right? Not necessarily; in some cases, a fracture's location in a bone could have implications for whether the horse will return to his previous level of work or if his career will be cut short. A research team recently examined the impact of a stress fracture's location within the humerus (the bone located between the shoulder and elbow joints) on racing prognosis. Nicole Fawns, DVM, a fellow in the Comparative Orthopaedics Research Laboratory at the University of Pennsylvania School of Veterinary Medicine, presented the results.

"Stress fractures are a major cause of lameness and result in significant economic loss within the Thoroughbred racing industry," Fawns explained. "The objectives of this study were to characterize stress fractures in the humerus and to describe post-injury racing performance."

Fawns and colleagues completed the retrospective study at Rood & Riddle Equine Hospital, in Lexington, Ky., using medical

records from 88 Thoroughbred racehorses referred to the clinic from 1990 to 2010. Each horse had been diagnosed with a humeral stress fracture via radiography or nuclear scintigraphy (bone scan).

"The influence of fracture location on racing performance was made by evaluating total earnings, total starts, average earnings, highest class raced, and length of time from injury to next race," Fawns added. Key findings included:

- Seventy-four percent of affected horses raced after fracture recovery;
- A greater percentage of horses that raced pre-injury raced after recovery than horses that did not race prior to injury;
- The average length of time between injury and racing following recovery was 285 days;
- The location of the lesion within the humerus and affected forelimb had "no significant influence" on the majority of racing variables evaluated;
- Horses started significantly more races after injury, but overall the horses returning to the track raced in a lower class than they did prior to injury;
- Average earnings per start decreased significantly post-injury; and
- Bilaterally affected horses (those with stress fractures in both legs) had "identical" fracture locations in both legs.

"Our results indicate that humeral stress fracture—regardless of location or limb affected—had a negative impact on racing performance but did not preclude return to racing," Fawns explained. "The significant drop in class, increase in number of starts, and decrease in average earnings is multifactorial; (other) variables—including increasing age—negatively affect racing performance."

Intravenous PBZ Dosing in Horses

While phenylbutazone (PBZ), commonly known as "Bute," is one of the oldest and most commonly used non-steroidal anti-inflammatory drugs (NSAIDs) in horses, studies about optimal dosage are scarce in the scientific literature. Working to further cumulative veterinary knowledge about Bute dosing, Jonathan Foreman, DVM, MS, Dipl. ACVIM, and his colleagues at the University of Illinois, measured the pain relief that varying doses of intravenous (IV) PBZ generated.

The research group used an adjustable heart-bar shoe model to produce lameness in study horses. By applying adjustable amounts of frog pressure via the turn of a screw, this model produces an on-demand, immediately reversible, NSAID-responsive lameness. Because investigators can produce and remove lameness almost instantly, each horse can act as its own control, so pain measurements are less affected by individual variation among horses.

In Foreman's study, investigators measured pain by observing heart rate elevation and lameness score. Heart rate rose in the study horses in a dose-dependent manner with the level of pressure applied to the frog, mirroring the lameness score.

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For the purposes of this study, Foreman and his colleagues determined that a "single IV dose" of PBZ for a 1,000-pound horse would be 10 mL (2 g). Because veterinarians often adjust PBZ doses in the clinical setting—tapering a dose downward as lameness resolves or doubling the dose in severely painful animals—Foreman's team chose to study the following dosage groups: a negative (saline) control, half dose (1 g IV/1,000 lbs body weight), a single dose, and a double dose (4 g IV/1,000 lbs).

The researchers found that with the 2 g dose of PBZ, heart rate declined, indicating a reduction of pain, within three hours. Single and double doses both decreased heart rate and lameness scores, but there was no significant pain relief difference detected between the two doses, indicating that a single dose was just as effective in controlling pain as a double dose. The 1 g dose produced better pain relief than the negative control, but the effects on heart rate lasted only 80 minutes.

Foreman concluded that when dosing PBZ in the horse, "More is not better. Less is less effective."

It is advisable for horse owners to consult a veterinarian to determine an appropriate amount of PBZ for a given situation prior to administering the medication.

Combination Use of Bute and Banamine Not Recommended

A common approach to lameness in the equine athlete is NSAID treatments, using drugs such as Bute or flunixin meglumine (FM, Banamine) either alone or in combination. Foreman, also discussed the effect of these medications on lameness when used at a normal recommended dose and whether combining the drugs confers any special effects.

Using the same procedure used in the previous study he described, Foreman's team induced reversible lameness in eight Thoroughbred horses. After an hour of the shoe application, Foreman and his colleagues treated the horses with one or both drugs: PBZ at 4.4 mg/kg, FM at 1.1 mg/kg, or PBZ + FM at these same dosages. In line with findings from previous studies, the team found that peak effect of these drugs occurred four hours following administration.

The team measured heart rates as an indicator of pain. All NSAID treatments decreased heart rates for two to 10 hours after administration, while lameness scores decreased for 1.3-12 hours. Heart rate reduction indicative of pain relief lasted for 12 hours after giving FM alone and combining PBZ and FM. Lameness scores decreased more quickly for PBZ or PBZ + FM combo-treated horses than for FM. "No significant differences were noted between giving PBZ alone or combining FM with PBZ," Foreman concluded

Foreman reminded the veterinary audience that these drugs are not competition legal under FEI (Fédération Equestre Internationale) rules. As of Dec. 1, 2011, USEF (United States Equestrian Federation) rules allowed only one of seven USEF-approved NSAIDs, with combinations of NSAIDS no longer legal. "In an emergency such as a colic or eye injury," reported Foreman, "additional use of FM can be given at a standard dose only by a licensed veterinarian." Provided approved paperwork is filed, the horse is allowed to compete no sooner than 24 hours later.

One of the biggest concerns he mentioned is the increased risk of gastrointestinal and renal toxicity as a result of

administering PBZ and FM in combination. He commented, "Recent work from another laboratory showed that combining half-dose oral PBZ with full-dose intravenous FM for only five days resulted in frequent ulcers and decreased plasma total proteins, indicative of gastrointestinal ulceration." In the current study, Foreman showed that there is no benefit in effect from combining the two drugs, and he speculated that there is very likely to be increased toxicity if that combination is given over several days.

Foreman stressed, "Giving twice the normal dose may not cause the analgesic effect to persist up to 24 hours, while this higher dose is toxic to kidneys and an already stressed gastrointestinal tract." Since he found that combining NSAIDs achieved no better results than using either drug alone, Foreman stressed that there is no good reason to combine these NSAIDs.

PRP and Acellular Bone Marrow for Tendon/Ligament Injuries

Biologically derived therapies are rapidly gaining popularity, especially for treating equine tendon and ligament injuries, and veterinarians have been hard at work determining the best case and therapy selection, dosage, and frequency of administration for each. To this end, David Frisbie, DVM, PhD, Dipl. ACVS, ACVS-MR, of Colorado State University, presented a study in which he examined platelet-rich plasma (PRP) products derived from several body systems and acellular bone marrow aspirate (ABMA) for treating these injuries.

According to Frisbie, PRP is widely used, but current recommendations for treatment dosage, frequency, and timing of administration after tendon and ligament injury vary considerably. Other questions that are not yet clear for practitioners include: the minimum and maximum desirable platelet concentrations; whether to "activate" the PRP (which involves adding components such as calcium or thrombin, an enzyme involved in the blood clotting cascade, to increase platelet growth factor release); and how to select which clinical cases are most likely to benefit from PRP therapy.

Frisbie referenced previous *in vitro* studies showing that PRP and ABMA upregulate cartilage oligomeric matrix protein (COMP), an equine tendon component that allows the structure to exert proper force against gravity and the weight of the horse as he stands and moves. Frisbie also referenced work that showed an upregulation of the genes involved in tendon healing after PRP treatment.

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In the current study Frisbie and his team compared three commercially available PRP products—autologous conditioned plasma (ACP), Fibrivet, and fPRP—and ABMA with a plasma control. They examined the ability of each of the products to concentrate platelets, white blood cells, and several growth factors at an injury site. Platelets, normally viewed as the cells responsible for blood clotting, also release growth factors that aid in tissue production and healing. They also evaluated each product's effects on tendon tissue components (tenocyte proliferation and matrix production, both required to rebuild damaged tendon) after 72 hours.

Results were mixed. Only ACP promoted significant tenocyte and matrix proliferation, as compared to the control group. However, only fPRP increased platelet and growth factor concentrations significantly when compared with controls.

Many questions about biologically derived therapies remain, but in this particular study ACP appeared to have the most desirable effect for tendon healing. Frisbie indicated that more research is still needed in this area, particularly in determining dosing frequency and the "therapeutic window" (minimum and maximum concentration range that will provide benefit rather than harm) for these therapies.

Bone Marrow-Derived Stem Cells: Sternum vs. Ilium

As stem cell therapy has gained popularity in equine medicine, many researchers have debated stem cell source site. Researchers at Colorado State recently compared the use of bone marrow-derived mesenchymal stem cells from two sites on the horse's body to determine which might be most effective for treating specific soft tissue injuries.

According to Laurie Goodrich, DVM, PhD, Dipl. ACVS, stem cells are particularly useful for treating tissues such as joints and tendons, which lack regenerative capability due to a deficiency in local stem cell response. Stem cells have been derived from adipose tissue (fat) and bone marrow. However, for tendon healing, bone marrow-derived cells yield better matrix and collagen production, she noted.

The research team compared bone marrow-derived mesenchymal stem cells (BM-MSCs) from the two most common extraction sites in the horse: the sternum (breastbone) and the ilium (hip). For BM-MSC therapy to be effective, Goodrich said two aspects are crucial: using large numbers of cells (roughly 5-10 million cells/centimeter in tendon and 5-10 million cells/joint) and implanting the cells early during the critical period between the inflammatory and fibroblastic phases of healing.

Goodrich discussed previously noted advantages and disadvantages for each site. Advantages of using the sternum are that the bone marrow aspirate flows better into the syringe; the amount of aspirate is not influenced by age of the horse; and cells are easier to collect. Its disadvantages are that the site is close to vital structures (heart, lungs); and the collector must crouch under the horse.

Ilium advantages are that the practitioner doesn't have to crouch while obtaining cells; and there's no risk of jabbing the heart or lungs. However, it's more difficult to get adequate cell volume; the sample size is age-dependent; and ilial samples often result in unsuccessful culture.

Researchers and clinicians had also noticed that the cells from sternal samples appeared different from those in ilial bone marrow samples.

Goodrich's study sought to provide clinicians with better information to guide selection site and on whether the MSCs' health varied between separate samples or (fractions) of bone marrow drawn from a site at one time. Goodrich and her coauthors examined two sequential 5-mL

samples from both sternal and ilial bone marrow aspirates of seven horses (they "plated" cells/grew them in culture, referred to as a "passage"). They found that:

- The first fractions of both samples yielded the highest cell counts;
- The cells of the first fraction were no healthier than those of the second;
- The health of the sternal and ilial samples were the same;
- By the second and third culture passages, cell morphologies (structures) were similar between the two sites; and
- Aspirates greater than 5-10 mL produced insignificant increases to the nucleated cell count.

Goodrich noted the following limitations to the study:

- A relatively small number of horses was used;
- There was some variability in age and gender of the horses; and
- The team didn't calculate the cell-doubling times, although the measurement of cell numbers at each passage was more relevant.

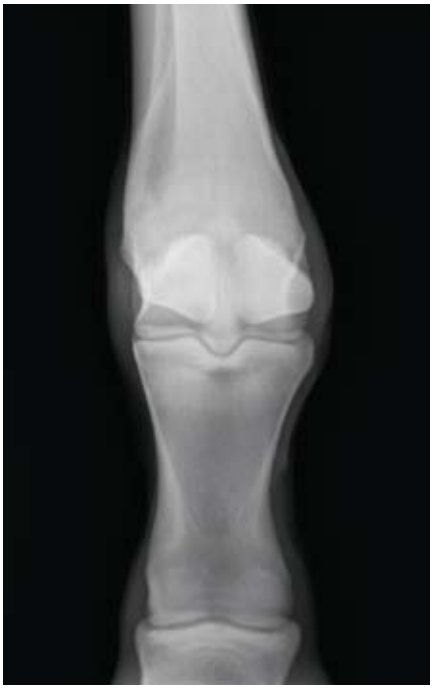
Goodrich's team concluded that the choice of bone marrow aspiration site should depend on clinician preference, since the cells of one site do not appear to be superior to the other.

Pastern Lucencies' Effect on Racing Performance

Prior to purchasing a racing prospect at a sale, a buyer typically has a veterinarian conduct a thorough examination, including a review of radiographs of the horse's limbs. Historically, many veterinarians have considered lucencies (also known as bone cysts) in pastern radiographs benign—namely, lucencies located on midline—however, one researcher has determined certain lucencies should be taken seriously because they appear to have a significant effect on racing performance.

Julie Vargas, DVM, described a retrospective study in which she and colleagues examined the impact of severe pastern lucencies in Thoroughbred yearlings on 2- and 3-year-old racing performance. Vargas, a practitioner with Equine Services LTD, in Wellington, Fla., noted that prior to this study the association between the presence of these lucencies and racing performance had not been evaluated.

Vargas explained that pastern lucencies typically occur on the weight-bearing surface of the joint; vary in size, shape, and depth; and can be caused by a variety of different factors, including developmental bone anomalies and/or trauma to the cartilage surface. They are detected more often in young male Thoroughbreds or Warmbloods, and they're most commonly found in the forelimb, she added.



COURTESY DR. JULIE VARGAS

Pastern lucencies located on the midline were the only type of bone cyst to negatively affect earnings per starts, total earnings, and number of starts in Vargas' study.

Vargas and colleagues at Rood & Riddle Equine Hospital examined 7,226 radiograph reports from Thoroughbred yearlings at auctions in the United States from 2002 to 2007. The team measured the lucencies and noted each abnormality's location within the pastern. Maternal siblings were used as controls. In total, the researchers evaluated 171 yearlings with lucencies, along with 832 siblings.

Upon reviewing the results, Vargas found that:

- Sixty percent of lucencies evaluated occurred in the hind limbs, while 40% occurred in the forelimbs (a statistic contrary to previous reports);
- Thirty-nine percent of affected horses were colts and 61% were fillies (refuting previous reports of males being more commonly affected);
- Ten percent of affected yearlings had lucencies in two limbs;
- There was no significant difference in the number of starts at 2 or 3 years, total earnings, or earnings per start between control horses and horses with lucencies located on the condyle (bulbous bottom or distal end of the bone) or facet (the smooth articular surface) of the long pastern;
- There was a significant difference between controls and horses with lucencies on the midline of the pastern. At 2 and 3, these horses had decreased earnings per start and decreased total earnings as compared to controls. Additionally, starts at 2 were fewer than controls.

"It is also feasible that horses with large severe midline (pastern) lucencies race successfully," Vargas added, reminding that in general, "pastern cysts seldom cause lameness and so a direct relationship between midline cysts and decreased performance is unlikely. The reason for decreased performance with midline pastern cysts is unknown."

Vargas noted that midline lucencies are "often believed to be normal variations of synovial fossas (nonarticulating areas in synovial articular surfaces)" and, thus, aren't noted on all radiograph reports. Vargas' research indicates it could be beneficial to note these lucencies more frequently.

"The ones that were noted (and, thus, the ones evaluated in the study) were therefore severe in nature and evident on multiple radiographic views," she added.

"This is part of the ongoing research at the Rood & Riddle Equine Hospital to better define the significant radiographic findings seen on sale radiographs both at public auction and on purchase examinations," Vargas concluded. "Only when we research a radiographic finding like pastern lucencies do we know the implications of those findings on the expected performance of the horses we are evaluating."

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