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Recent Advances in Diagnosis of Equine Joint Disease

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INTRODUCTION

While osteochondral fragmentation, fractures, subchondral bone disease, osteoarthritis, and osteochondritis dissecans (OCD) are common in the horse, diagnosis of these diseases usually occurs only after the disease has become established. The detection of early or subtle disease in the past has been poor, but the situation is improving. Clinical examination and radiographic imaging are still the most commonly used techniques for diagnosis of osteochondral disease, yet osteochondral damage seen during arthroscopic surgery is usually more severe than that seen on radiographs. It is the author's subjective opinion that there is commonly a good correlation between the severity of clinical symptoms (principally lameness and synovial effusion) and the amount of damage or disease found at arthroscopy of joints. However, it has been reported in humans that, while the most common complaint of patients with osteoarthritis is pain, only about half of the patients with radiographic osteoarthritis have symptoms (Hochberg et al., 1989). The reason that half of the patients with radiographic osteoarthritis have or do not have pain is not always clear since only some of the causes of pain have been researched (Altman and Dean, 1989). It is recognized that there is no "diagnostic test" for osteoarthritis in man (Altman, 1997), but focus on MRI and biomarkers has occurred in recent years.

Human clinical trials are now very specific about the recording of outcomes measures. Outcome variables in osteoarthritis clinical trials need to be selected on the basis of the therapeutic objective and are a critical part of assessing the results of medication. In a workshop of the World Health Organization (WHO) and the American Academy for Orthopedic Surgeons, the methods to assess progression of osteoarthritis of the hip and knee were reviewed (Dieppe et al., 1994). In addition, the European Group for the Respect of Ethics and Excellence in Science (GREES) has made recommendations on methods for registration of drugs for osteoarthritis (GREES, 1996). We are equally in need of objective outcome parameters in assessing the results of various treatments for musculoskeletal disease in general and joint disease in particular in the horse.

Diagnostic Techniques Used in the Horse

Clinical examination is still critical. Imaging techniques include radiography, nuclear imaging, computer tomography (CT), magnetic resonance imaging (MRI), and ultrasonographic examination. Conventional synovial fluid analysis is still used to define infection, but more recent work with synovial fluids and serum biomarkers offers real potential for diagnosis of early change in cartilage and bone. Arthroscopy is still the gold standard for diagnosis of cartilage defects, as MRI is limited by resolution, particularly in the thin cartilage of the carpus and the fetlock. On the other hand, MRI has been useful for more extensive changes in soft tissues and bone.

Clinical examination

Assessment of joint effusion, range of motion, joint capsule thickening, and pain with flexion are currently used and subjectively graded by veterinarians doing lameness examinations. The lameness grading guidelines set up by the AAEP are used frequently (AAEP, 1991). While flexion tests are commonly used, the reliability of such tests is controversial. Confounding factors make this objective evaluation of an individual for pain difficult. The principal ones are differences in observer scores and differences in a particular subject's tolerance to pain. The same is true for a horse. Motion analysis has been employed as a research tool. The characteristics of limb movement and force can be determined. Abnormalities in these parameters can be characterized in patients with disease (Craik and Otis, 1995). As an example, it has been found in humans that impulsive loading often leads to osteoarthritis (Radin and Rose, 1986). Because data analysis involves sophisticated, expensive equipment and is often labor intensive, most gait analysis in veterinary medicine occurs in the research field.

Motion analysis systems that combine data from force plates, EMG analysis and muscle forces, and kinematics can provide sensitive information to an individual's movement (Radin and Rose, 1986), and these systems have been extensively studied in humans and are used clinically to evaluate an individual's gait. Limb use and muscle forces play a large role in joint loading (Bassey et al., 1997), and recent work from our laboratory in the horse has shown this. For instance, in measuring contact forces across the carpus at the trot, the peak ground reaction force is 1,350 pounds, whereas the peak muscle forces are 2,700 pounds, leading to a total joint force of 4,050 pounds. In other words, muscle forces are two times ground forces (Brown et al., 2003a; Brown et al., 2003a,b). Diagnostic techniques that describe kinematics and muscle forces potentially allow clinicians to identify those individuals with problems related to movement and potentially modify that. At present it is a research tool.

We have also evaluated the use of thin-film sensor systems to evaluate limb loading in horses. The system was attractive because it could be attached to the bottom of a horse's hoof to measure force distribution throughout the sole surface (Brown et al., 2003b), or it could be used like a force plate for jogging horses across. However, evaluation of the force plate-type system for accuracy and durability has shown it to be inadequate.[a] Preliminary results indicate, however, that using an "in-shoe" system for the sensor film deploys results similar to the force plate.[b]

Computer models

Computer models of joint loading have been studied in both humans and animals. Modeling is the computer-based mathematical representation of the skeleton, ligaments, and muscles used to calculate forces in muscles and joints. The principle is to develop the model based on kinematic parameters and compare that model to those developed from imaging techniques such as computer tomography (CT) and magnetic resonance imaging (MRI). Muscle, tendon, ligament, and ground reaction forces in tissue properties can be inserted into the model. Once developed, imaging-based modeling can be performed so that subtle changes in joint geometry and loading can be detected with the ultimate goal of developing long-term models in which data can be continually added. The clinical goal is to develop

patient-specific models that allow abnormalities in loading and tissue response to be detected (Pandy et al., 1998).

An example of the use of modeling is a current project whereby finite element modeling is being used as potential screening for susceptibility for condylar fracture in the fetlock joint.

Radiographic examination

Radiographic examination is still the most widely used imaging technique for the diagnosis of osteochondral disease, but it is an insensitive method of diagnosis. Articular cartilage cannot be viewed radiographically except when there is extensive loss and decreased joint space, and 30-40% change in bone mineral density is required before bone changes can be appreciated (Greenfield, 1986). In addition, multiple images are required for evaluation of a three-dimensional structure. Disease is often recognized after significant damage has occurred. This lack of sensitivity can prevent early and accurate diagnosis. Measuring joint space is fraught with error (Adams and Wallace, 1991). The significance of osteophytes is frequently unrelated to intra-articular pathological change and considerable change in bone density is necessary to identify sclerosis and erosion. In a study correlating radiographic and histologic changes in the tarsi of horses, Laverty et al. found that radiographs were insensitive for detecting subchondral bone sclerosis and erosion when compared to histology (1991). It has also been pointed out that superimposition of osteophytes may appear as sclerosis (Widmar and Blevins, 1994).

Computed tomography

Computed tomography (CT) has had increased use in the horse, both as a research and clinical tool. Benefits are visualization of the area of interest in three dimensions (which alleviates superimposition problems) and the ability to determine density patterns quantitatively with three-dimensional osteoabsorptiometry. Differences at the parasagittal groove of the distal metacarpal condyle have been recognized and such density gradients may warn against incipient condylar fracture.

Density patterns of bone can be determined by three-dimensional modeling of CT images (CT osteoabsorptometry, CTO). CTO allows three-dimensional evaluation of the joint in any plane. Houndsfield units, which are the CT measure of bone density, are determined and coordinated into ranges and then the ranges of density are represented by colors. This color map is then superimposed over a three-dimensional image of the joint surface to show a representation of the relative subchondral density. The use of a density phantom has allowed for objective measures of density to be determined. Because it has been shown that stress distribution within an osteochondral section is related to the density pattern, it can be concluded that the subchondral density pattern is the representation of the loading history of the joint (Muller-Gerbl et al., 1989). Considerable work has been done in our laboratory by Kawcak. Initially, the subchondral density patterns of bones in equine carpal and metacarpophalangeal joints were established. Since that time, the effects of exercise in young horses where exercise was commenced in foals at 3 weeks have been followed and compared to those in pasture-reared horses. In addition, we have evaluated the changes in bone density patterns with age.[c]

Researchers identified substantial density gradients between the denser subchondral bone of the condyles and the subchondral bone of the sagittal groove in the distal MCIII and MTIII with a view to explaining the etiology of distal condylar fractures. These density gradients were shown to equate to anatomical differences in loading intensity and locomotion, and it was hypothesized that such difference in bone density results in stress concentration at the palmar/plantar aspect of the condylar groove, which may predispose to fracture (Riggs et al., 1999a). In a companion paper, linear defects in mineralized articular cartilage and subchondral bone were found in the palmar/plantar aspects of the condylar groove, adjacent to the sagittal ridge (Riggs et al., 1999b). These were closely related to the pattern of densification of subchondral bone and were associated with intense focal remodeling of the immediate subjacent bone. Parasagittal fractures of the condyles originated in similar defects. This work and subsequent examination of CTs in our laboratory have demonstrated a potential to diagnose incipient condylar fractures in the racehorse.

Magnetic resonance imaging (MRI)

Results from human studies have shown that MRI is a sensitive and specific imaging tool for examination of hard and soft tissues in joints and that it is as good as, if not better than, arthroscopy for detecting subchondral lesions (Reeve et al., 1992). MRI is the best measure of articular geometry and more recently an ability to quantify articular cartilage matrix properties using contrast enhancement has been demonstrated (Bashir et al., 1997). Postmortem MRI and other imaging modalities, including clinical examination, radiographs, nuclear centrigraphy, and arthroscopy, were used to evaluate an osteoarthritic metacarpophalangeal joint in a horse (Martinelli et al., 1996). Kawcak et al. (2001) have also used this technique to evaluate the effects of exercise on subchondral bone of horses and found that it could image osteochondral damage, including small fragments (Kawcak et al., 2001).

More recently, there have been reports of the clinical use of MRI (high-field strength) in anesthetized horses to diagnose specific changes in the distal limb (Schneider, 2002; Dyson et al., 2005), and a paper on the use of a low-field strength standing MRI to image the distal limb has been reported (Mair et al., 2005).

We have had a high-field strength MRI at CSU for 4 years, and it is being used regularly on clinical patients to diagnose problems from the tarsus and carpus down very effectively. Changes in the joint capsule and ligaments associated with joints can be diagnosed equally well to those in articular cartilage and bone.

Ultrasonographic examination

Ultrasonographic examination of joints was pioneered by Denoix (Denoix, 1996). The technique can be used to evaluate soft tissues associated with the joint, including collateral ligaments, joint capsule, other associated ligaments, and menisci (Marks et al., 1992). The use of ultrasonography to image the medial palmar intercarpal ligament in the carpus has also recently been described (Driver et al., 2004).

Nuclear scintigraphy

Nuclear scintigraphy, also known as gamma scintigraphy or bone scan, has been extremely helpful in detecting cortical bone disease and stress fractures in horses. Its most significant use, in my opinion, has been in detecting stress fractures of the pelvis, tibia, femur, and humerus prior to them becoming complete fractures. A nuclear scintigraphic image shows the physiologic distribution of radioisotope throughout the bone and therefore is more sensitive than radiographs in detecting early osteoarthritis in human knees (McCrae et al., 1992). In humans, nuclear scintigraphy has been the best early predictor of joint space narrowing in knees (Dieppe et al., 1993) and in some cases has been more sensitive than arthroscopy and MRI for detecting early and subtle subchondral bone pathology (Marks et al., 1992). One problem that has been identified, however, is the inability of nuclear scintigraphy to distinguish stress response due to subchondral bone adaptation from osteochondral damage. Osteochondral fragments show up as discrete focal areas of increased radioisotope uptake (Parks et al., 1996), but any remodeling change due to stress will also show increased uptake of radioisotope (Chambers et al., 1995). Because of this, mild to moderate increases in uptake of radioisotope in the joints of horses, especially young, exercising horses, can lead to confusion. However, scintigraphy can be used as a screening tool, but it needs to be recognized that while sensitive, it is not sensitive enough to demonstrate a specific anatomical problem.

More objective means of assessment have been used to eliminate some of the subjectivity with nuclear scintigraphy. Using computer programs, areas of particular interest can be highlighted, the counts/pixel determined for that area, and normalized to the counts/pixel for a reference area within the same limb (Wittbjer et al., 1982). This is of particular benefit because the distribution of radioisotope within an area varies between animals and between different regions within the same animal. If we outline an area of interest such as the distal condyles of the third metacarpus and then normalize the count to a reference area such as the cortical area of the first phalanx, it is possible to eliminate the influence of individual horse uptake in assessing this area. Care needs to be taken to ensure the reference area is normal and has no increased uptake compared to the surrounding bone. This technique takes into account the regional limb response to exercise and therefore potentially reduces the effect of exercise-induced increases.

This is a valuable diagnostic technique that is very sensitive but somewhat nonspecific. However, specific localization of some osteochondral lesions can be seen. Nuclear scintigraphy is very helpful in detecting cortical bone disease and in particular, stress fracture in upper limbs (humerus, tibia, femur, and pelvis) that cannot be detected with radiography. They are also more sensitive than radiographs in detecting human knee osteoarthritis, and it is possible to detect early osteochondral lesions and "prefracture" disease.

Optical coherence tomography

Histologic properties of osteochondral tissues can be assessed using optical coherence tomography (Hermann et al., 1999), and this has been likened by Kawcak (2001) to an in vivo form of biopsy. In

humans, optical coherence tomography has shown a fairly good correlation between images and histologic change (Billinghurst, 2003).

Biomarkers

Imaging biomarkers. Recent work at the CSU Orthopaedic Research Center has defined uses of imaging biomarkers, at least in experimental osteoarthritis, including increase in radiographic lysis, increase in nuclear scintigraphic uptake, minor change in subchondral sclerosis on CT, and an increase in subchondral bone edema on MRI that correlates with type I and II collagen biomarkers. This was in experimental osteoarthritis, but it sets guidelines for clinical use.

Fluid biomarkers. Synovial fluid and serum are used as biomarkers because cartilage degradation involves destruction of the collagen framework and loss of proteoglycan (breakdown in synthesis) products of type II collagen, and proteoglycans are liberated in increasing concentrations into the synovial fluid and ultimately the serum.

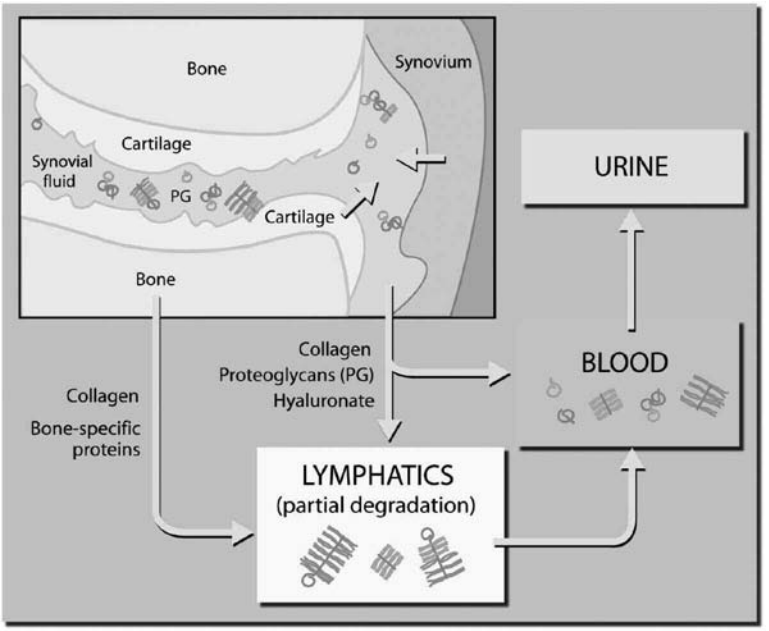

Figure 1. Principle of synovial fluid and serum biomarkers.

Fluid biomarkers can be divided into synthetic and degradative markers, and both are useful in diagnosing early change in cartilage and bone. Figure 2 is an example of the principle whereby antibody-based biomarkers can detect early collagen degradation (Ray et al., 1996; Billinghurst, 2003; McIlwraith, 2005a).

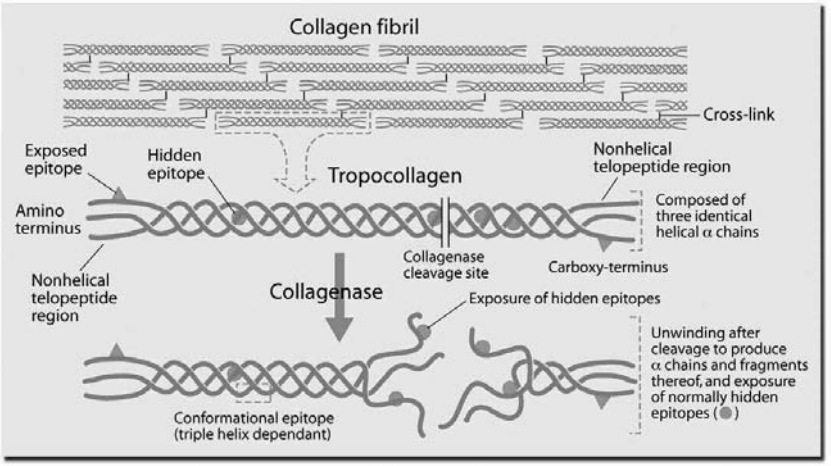

Figure 2. Principle of antibody recognition of collagen degradation.

Clinical studies have demonstrated usefulness of serum biomarkers in diagnosing early equine joint disease (Frisbie et al., 1999; McIlwraith 2005b), defining the clinical significance of OCD (Laverty et al., 2000; Billinghurst et al., 2004), and detailing changes in exercise and changes in osteoarthritis that can be differentiated from change in exercise (Frisbie et al., 2008). In the most recent study we have done at CSU, we have analyzed serum biomarkers and shown potential usefulness in the early prediction of intra-articular fractures, as well as stress fractures and injury to tendons and ligaments (Frisbie et al., 2009).

More recently, work with gene chip microarray and proteomics provides the potential of adding tests for a clinical biomarker panel.

FOOTNOTES

a) Betavet Soluspan®, Schering-Plough Animal Health Corp., Union, NJ 07083.
b) Perino, V., C.E. Kawcak, D.D. Frisbie, et al. 2005. Unpublished data.
c) Shearin, M. 2005. Ph.D. dissertation. Colorado State University, Fort Collins, CO.

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