THE PENNSYLVANIA STATE UNIVERSITY
SCHREYER HONORS COLLEGE

DEPARTMENT OF ANIMAL SCIENCE

CARTILAGE INJURY REHABILITATION IN THE HUMAN AND IMPLICATIONS FOR USE IN EQUINE REHABILITATION PROTOCOLS

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SPRING 2013

A thesis
submitted in partial fulfillment
of the requirements
for a baccalaureate degree
in Animal Sciences
with honors in Animal Sciences

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ABSTRACT

Human and equine articular cartilage is remarkably similar in its structure and function. The cartilage structure is designed to support load-bearing forces on the joint, but forces that exceed the capacity of the cartilage can lead to damage of the cartilage matrix and chondrocyte apoptosis. Articular cartilage has a poor healing ability, and damage to the cartilage matrix lead to the development of osteoarthritis. Osteoarthritis is more common in athletic populations of both humans and horses since their joints are subjected to increased forces during physical activity.

Articular cartilage injuries have been long studied in order to develop surgery and rehabilitation protocols that will give the patient the greatest chance of return to normal, pain-free function. Common surgical procedures include debridement, abrasion arthroplasty, microfracture, autologous chondrocyte implantation (ACI), and autologous osteochondral mosaicplasty (OATS). The surgical procedures are very similar for both humans and horses. However, rehabilitation programs following these procedures vary greatly between the human and equine species. In human medicine, rehabilitation programs are individualized based on the patient, the size and severity of the defect, and the surgical procedure used to correct the defect. These programs center on the use of range of motion exercises and a gradual return to weight bearing in order to optimize the patient's return to normal physical activity following surgery. Equine rehabilitative therapies involve immediate return to full weight-bearing following surgery and include periods of stall rest during which movement is restricted.

The similarities between human and equine cartilage physiology and the surgical procedures used to treat osteoarthritis and cartilage defects lend researchers the opportunity to utilize advances and results from human medicine in equine veterinary care. Use of techniques such as underwater treadmills to minimize weight bearing following surgery may be a step towards optimizing the equine athlete's return to performance following injury.

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Cartilage Structure, Function, and Injury

Introduction

The human and equine cartilage is remarkably similar, providing the opportunity to utilize the research and progress made in one species to benefit the cartilage repair and rehabilitation of the other species (Frisbie et al., 2003; Frisbie et al., 2006). Human medicine can take advantage of the ability of their patients to reduce weight bearing and follow strict rehabilitation protocols. However, limitations on the exercises and management practices that can be used in equine medicine force practitioners to adapt their programs in order to provide their patient with the best possible chance at recovery while working in the realm of reality. Utilizing technology such as aquatic therapy may give equine practitioners a way to work within their patient's abilities while providing an optimal environment for cartilage rehabilitation (King et al., 2013). The purpose of this paper is to identify the rehabilitation protocols utilized in human and equine medicine and ways in which equine management and medicine practices can be altered to encourage proliferation of repair tissue following surgery. This can only be done by having an understanding of cartilage physiology and injury pathways within the body and by understanding the surgical procedures utilized to correct cartilage defects and how to change rehabilitation programs based on the operation utilized.

Cartilage Structure

The articulating surfaces of a diarthrodial (synovial) joint are covered in hyaline cartilage. Hyaline cartilage is characterized by its molecular composition which lends itself to providing a highly elastic load-bearing surface that supports the joint during movement or weight-bearing (Mithoefer et al., 2012). The cartilage also provides a low-friction surface so the articulating surfaces can slide past each other (Shi et al., 2012). Normal articular cartilage is composed of chondrocytes that synthesize an extracellular matrix consisting primarily of collagen and proteoglycans (Cohen, 1998). Interestingly, human and equine cartilage has a very similar composition and is of comparable thickness (Frisbie et al., 2003; Frisbie et al., 2006). By wet weight, cartilage is composed of 68-85% water, 10-20% collagen (mostly type II collagen), 5-10% proteoglycans, and other minor components such as chondrocytes, link proteins, salts, and other forms of collagen (Mow and Huiskes, 2005). This composition is responsible for the mechanical properties of articular cartilage.

Scattered among the articular cartilage matrix are chondrocytes, which are responsible for the production of collagen and proteoglycan molecules that form the extracellular matrix (Jerosch, 2011). Chondrocytes occupy 1-5% of the volume of the cartilage but are critical components because they are responsible for the production, organization, and degradation of the extracellular matrix (Mow and Huiskes, 2005; Jerosch, 2011). These pathways for matrix production by chondrocytes are stimulated by factors such as compression, interstitial pH, and changes in hydrostatic pressure (Gray et al., 1988; Parkkinen et al., 1993).

The collagen matrix of articular cartilage is responsible for maintaining the shape and tensile strength of the cartilage tissue (Schmidt et al., 1990). Between 90-95% of collagen in articular cartilage contains type II collagen fibers (Buckwalter and Mankin, 1997). Type II collagen fibers are heavily cross-linked. These links are strengthened by the presence of type IX and XI collagen (Mendler et al., 1989). These fibers are synthesized and secreted by the chondrocytes in a complex process involving synthesis within the endoplasmic reticulum and modification to form a triple-helical molecule before being secreted from the cell (Mow and Huiskes, 2005). While the exact roles of these fibers is not known, it is understood that they are necessary for proper cartilage structure because a mutation in the genes responsible for the production of type II, IX, and XI collagen results in defects in the formation of the cartilage matrix (Eyre, 2002). During osteoarthritis, the chondrocytes are signaled by the surrounding matrix to produce type II collagens. Type III collagen fibers differ in their structure and cause a weakening of the cartilage matrix (Aigner et al., 1993). Therefore, healthy hyaline cartilage and osteoarthritic cartilage can be differentiated based on the proportion of type II and III cartilage within the matrix (Aigner et al., 1993). The goal of the surgical and rehabilitation procedures is to encourage the growth of tissue that will support the production of type II collagen fibers and the normal hyaline-like articular cartilage (Brittberg et al., 1994; Steadman et al., 2001)

The articular cartilage is composed of four layers, or zones. These include the superficial, middle, deep, and calcified cartilage layers (Mow and Huiskes, 2005). The collagen fibers in the matrix are arranged in different patterns based

on their location within the cartilage (Figure 1). Fibers in the superficial zone run parallel to the articular surface. In the middle zone of the articular cartilage, these fibers are less organized. Fibers in the deep zone of the cartilage are perpendicular to the subchondral bone and extended from within the subchondral bone, through the calcified cartilage layer, and into the lower portion of the articulating cartilage to anchor the articular cartilage to the subchondral bone (Clark, 1985). These layers of collagen fibers are responsible for holding proteoglycan aggregates in place to maintain swelling pressure within the cartilage matrix, provide the cartilage with compressive strength, and maintain the articular cartilage shape and tensile properties (Pottenger, 1982; Schmidt et al., 1990).

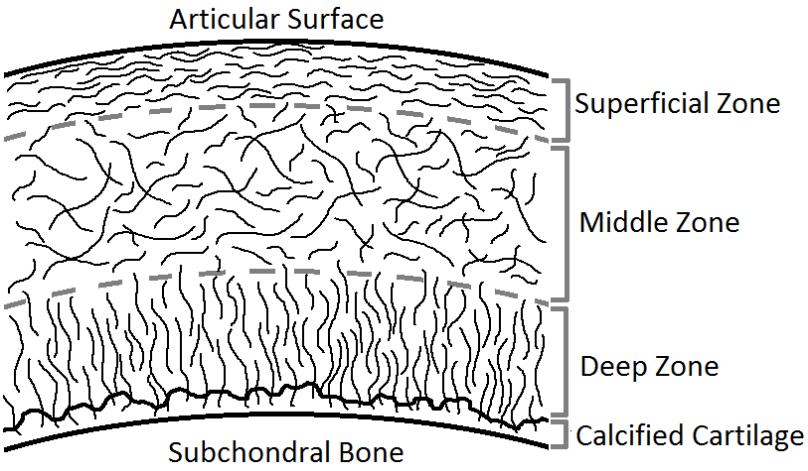

Figure 1. Schematic representation of the layers of the articular cartilage highlighting the orientation of the collagen fibers in the various layers of the cartilage.

Proteoglycans are large, charged molecules that are responsible for creating swelling pressure within the joint and giving cartilage the ability to hold water (Jerosch, 2011). Proteoglycans are composed of a core protein with chains

of the glycosaminoglycan molecules chondroitin sulfate (CS) and keratin sulfate (KS). These proteoglycan molecules can be linked to hyaluronan by glycoproteins (link proteins) to form huge aggregates (Figure 2) (Hardingham and Fosang, 1992). Retention of the proteoglycans within the extracellular matrix is dependent upon the integrity of the collagen mesh because when the mesh is damaged, the proteoglycan aggregates are able to escape from the matrix (Pottenger, 1982). The negative charges of the CS and KS molecules branched on the proteoglycans repel each other and the charges attract positive molecules such as Na^+, which draws water into the tissue. These molecular interactions are what create the swelling pressure within articular cartilage (Eisenberg and Grodzinsky, 1985). This swelling pressure within the collagen matrix is responsible for the load-bearing abilities of the articular cartilage (Mow et al., 1980).

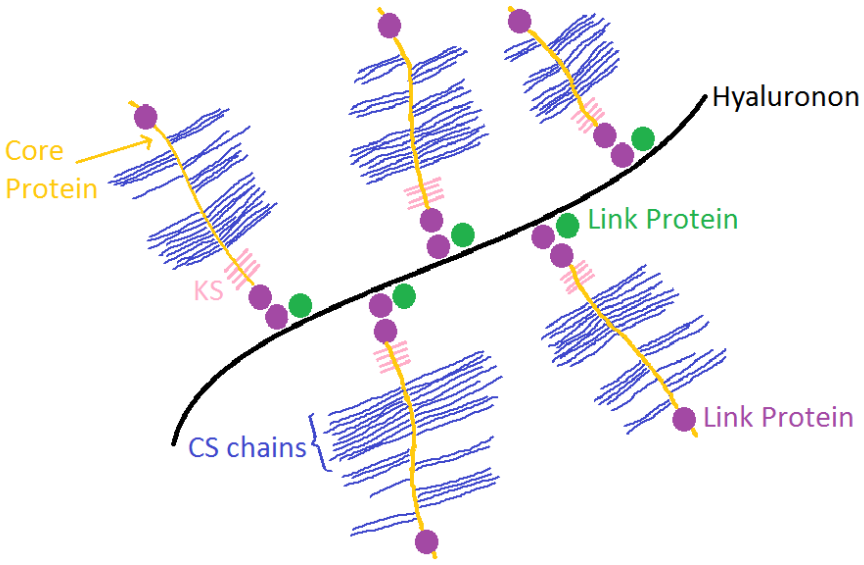

Figure 1. A schematic representation of a proteoglycan aggregate. Proteoglycans consist of CS and KS chains attached to a core protein. Aggregates form when link proteins attach proteoglycans to a central hyaluronic acid (hyaluronan) filament (Hardingham and Fosang, 1992)

Cartilage Function

Cartilage plays a key role in the function of the diarthrodial joint by providing a low-friction surface that supports load-bearing forces (Setton et al., 1990; Sang-Soo et al., 2012). The low-friction environment provided by cartilage allows the bones associated with the joint to slide past each other without harm to the surface of the bone. Following injury and during degenerative conditions such as osteoarthritis there is increased friction within the joint (Sang-Soo et al., 2012).

The surface of the articular cartilage prevents exudation of the interstitial fluid from the cartilage and maintains the fluid pressurization that supports weight bearing (Setton et al., 1990). The combination of the solid matrix and the high water and fluid content give articular cartilage a biphasic nature that is responsible for its load-bearing properties. Compression of the articular cartilage causes a change in the volume and shape of the cartilage. This results in a change of pressure that redistributes the interstitial fluid and causes a diffusional drag as water and ions flow through the porous solid matrix (Mow et al., 1980). Interstitial flow of fluid through the porous collagen matrix, frictional drag as water and ions move through the fluid, and the pressurization of fluid within the cartilage allow mechanical forces to be transferred between the solid and liquid phases during movement to provide load support to the joint (Setton et al., 1993). Damage to the articular cartilage surface causes a loss of fluid pressurization and disturbs the function of the load-bearing mechanisms, impeding the ability of the articular cartilage to distribute compressive forces (Mow et al., 1980).

Injury

Under normal conditions, the articular cartilage is able to support weight bearing and frictional forces. However, excessive force may damage the articular cartilage matrix or may cause apoptosis of the chondrocytes within the matrix (Zhang et al., 1999; Loenig et al., 2000). Articular cartilage lesions have minimal healing capacity due to the avascular and aneural nature of cartilage, and lesions may progress to osteoarthritis (Buckwalter, 1998; Hunziker, 2002). The inability of articular cartilage to self-repair following injury is what creates the need to develop effective surgical treatment and rehabilitation programs in order to improve the quality of life of patients following cartilage injury.

The magnitude and type of force that causes damage to the cartilage matrix will determine the size of the defect that is created (Jeffrey et al., 1995; Buckwalter et al., 1998). The time between the initial injury and when the patient seeks treatment may also impact the size of the defect, as damage to the chondrocytes causes matrix degradation and creates a downward spiral as the matrix is weakened and is subject to increased risk of injury (Loenig et al., 2000) Ultimately, the extent of the damage to the cartilage is important because the size of the defect will be a factor in determining the surgical repair technique used (Brittberg et al., 1994; Cameron-Donaldson et al., 2004; Bartha et al., 2006; Laupattarakasem et al., 2009; Mithoefer et al., 2012).

While injury to the articular cartilage may not impact the other soft tissues of the joint, damage to the tendons, ligaments, and muscles supporting the diarthrodial joint may negatively impact the articular cartilage (Setton et al., 1994; Buckwalter, 1998; Jerosch, 2011). Direct blunt trauma, indirect impacts, or torsion of the joint can cause

damage to the articular cartilage of a joint or the subchondral bone without impacting the other soft tissues of the diarthrodial joint (Buckwalter, 1998). Injury to other soft tissues can cause joint movement outside of the normal range of motion, leading to increased pressure on the hyaline cartilage due to uneven load distribution (Jerosch, 2011). Damage to the articular cartilage caused by uneven load distributions can cause matrix deformation and loss of matrix stiffness. This damage also causes a loss of proper load support in the joint when the articular surface is damaged and proteoglycans and water molecules escape from the matrix. (Setton et al., 1994).

The development of osteoarthritis is a result of a downward spiral that starts with a causal incident and develops as the matrix loses its ability to handle compressive forces and the chondrocytes undergo apoptosis and can no longer maintain the articular cartilage. Acute loading of the joint may cause damage to the tissue matrix or to the articulating surface of the joint (Loenig et al., 2000; Maroudas, 1976; Setton et al., 1993). In vitro studies of articular cartilage show that at low impact force, the superficial layers of the cartilage are damaged, and as the impact stress increases progressively deeper layers are damaged (Zhang et al., 1999). Damage to the cartilage matrix makes it more susceptible to damage from following impacts. If the bone-cartilage interface and articular surface are intact, the cartilage is able to prevent fracture by transmitting some of the shock to the underlying bone. However, fractures in the cartilage prevent the transmission of the force, reduce the support from the underlying bone, and increase damage to the cartilage (Jeffrey et al., 1995).

The hydration of cartilage depends on the balance between swelling pressure created by the proteoglycans and tensile force exerted by the collagen network. As

damage to the collagen matrix occurs, elastic restraint on the swelling pressure within the joint decreases and the tissue swells as more water is able to move into the cartilage toward the charged proteoglycans. This leads to increased hydration despite any proteoglycan content that may have been lost after damage to the matrix (Maroudas, 1976; Jeffrey et al., 1995). Swelling of the cartilage hinders the ability of the fluid mechanisms to support weight and increases stress on the collagen matrix (Setton et al., 2003).

Trauma to the chondrocytes is another method through which cartilage degradation occurs. Chondrocyte sensitivity to joint loading varies, but a small percentage of chondrocytes are sensitive even to loads below the stress levels necessary to alter biomechanical properties of the matrix and cause proteoglycan release and tissue swelling (Loenig et al., 2000). As the chondrocytes sensitive to low stress apoptose, the surrounding matrix is degraded and the structure is weakened. When matrix degradation is combined with further and increased load, further chondrocyte apoptosis occurs and more matrix is degraded (Loenig et al., 2000). This cycle of matrix damage, loss of load support, chondrocyte apoptosis, and further matrix degradation creates the need for surgical correction to replace the damaged matrix and chondrocytes in the site of injury (Buckwalter, 1998).

Osteoarthritis in Athletic Populations

Increased activity has been associated with increased risk of developing osteoarthritis (Kujala et al., 1994. Increased incidence of osteoarthritis has been seen in populations of professional athletes who participate in sports ranging from endurance-

type sports such as long-distance running to sports such as soccer that involve sprinting and turning and high-load bearing sports such as weight lifting (Kujala et al., 1994) Studies of professional soccer players in England have shown that 29-49% of retired soccer players are medically diagnosed with osteoarthritis (Kujala et al., 1995; Drawer and Fuller, 2001; Turner et al., 2000). In one of these studies, the knee was the location of 46% of acute career-ending injuries and 37% of chronic career-ending injuries. Twenty-one percent of the acute injuries were damage to the cartilage (Drawer and Fuller, 2001). The prevalence of osteoarthritis in top-level athletes of other professions was 31% in weight lifters and 14% in runners. Soccer players were shown to have the highest prevalence of tibiofemoral osteoarthritis, and weight lifters had the highest prevalence of patellofemoral osteoarthritis (Kujala et al., 1995). This data shows that the knee is the major site of cartilage injury in a wide variety of human athletic sports such as soccer, running, and weight-lifting.

Like the human, equine athletes are at higher risk for developing impact trauma-induced osteoarthritis. In a study of 647 racehorses from beginning training as yearlings until their two year old years, there were 184 cases of carpal or metacarpal injuries in 165 horses (Reed et al., 2012). A study of 50 racehorses euthanized within 60 days of racing showed that one-third of all 2 and 3 year old horses had partial or full-thickness lesions within the articular cartilage (Neundorf et al., 2010). Career-ending injuries in human athletes are usually associated with knee trauma, whereas equine athletes most often suffer from damage to the carpal joint. Despite differences in the areas most affected by cartilage defects, the processes for surgical repair for horses are similar to those used in humans (Barnewitz et al., 2006).

Summary

- The articular cartilage is composed of an extracellular matrix of collagen and proteoglycans which are produced by chondrocytes scattered throughout the matrix (Cohen, 1998).
- The structure of articular cartilage and the flow of interstitial fluid through the cartilage matrix provides a low-friction surface between the articulating joints and gives the cartilage load-bearing properties (Setton et al., 1990).
- While the articular cartilage is designed to withstand impact and load-bearing forces, excess force on the cartilage can cause chondrocyte apoptosis or damage to the cartilage matrix (Zhang et al., 1999; Loenig et al., 2000).
- Damage to the cartilage matrix results in a vicious cycle in which the damaged matrix loses its load-bearing abilities and the chondrocytes have a decreased capacity for cartilage repair. This makes the cartilage more susceptible to injury from further impacts (Kujala et al., 1995)
- Because cartilage has limited ability for self-repair, surgical procedures are often needed (Buckwalter, 1998).
- Active athletic populations of humans and horses are more susceptible to articular cartilage damage than non-active populations (Kujala et al., 1994; Reed et al., 2012).
- The knee is the most common site of osteoarthritis in the human and the carpus joint is the most common site of osteoarthritis in the horse (Barnewitz et al., 2006).

Chapter 2

Articular Cartilage Repair Procedures

Multiple procedures exist for the treatment of post-traumatic articular cartilage repair. These procedures include debridement, abrasion arthroplasty, microfracture, autologous chondrocyte implantation (ACI), and autologous osteochondral mosaicplasty (OATS) (Reinold et al., 2006; Bedi et al., 2010; Steadman et al., 2001; Brittberg et al., 1994; Hangody et al., 2004). The use of each procedure depends on the site and severity of the injury. Microfracture is the most popular of the techniques used. In a study of 118 knee cartilage injury cases in the National Football League, 43% of injuries were treated with microfracture, 31% were treated with debridement, 6% were treated with the OATS procedure, and 3% were treated with chondrocyte-based repair such as ACI (Brophy et al., 2009). The procedure used to correct a defect depends on the size of the defect and the stage of osteoarthritis. Debridement and lavage of the cartilage is typically used in the early stages of osteoarthritis and does not correct the cartilage defect (Cameron-Donaldson et al., 2004; Laupattarakasem et al., 2009). The OATS procedure and marrow-stimulating procedures such as microfracture are used to correct small to midsize defects (1-4 cm^2) (Bartha et al., 2006; Mithoefer et al., 2012). ACI can be used on a wider range of defects and has been shown to restore joint function in patients with defects exceeding 6 cm^2 (Brittberg et al., 1994).

Debridement

The debridement procedure is often used in the early stages of osteoarthritis (Laupattarakasem et al., 2009). Its purpose is not to correct the cartilage defect, but to remove debris, loose cartilage, and inflammatory molecules which can cause cartilage degradation (Cameron-Donaldson et al., 2004). Unlike the other articular cartilage repair procedures, the subchondral bone is not abraded during the surgery (Ogilvie-Harris and Fitsialos, 1991).

In the debridement procedure, incisions are made into the joint for insertion of an arthroscope, inflow cannula, and the working instruments (Moseley et al., 1996). Fluid is lavaged through the joint while the surgeon removes areas of rough or loose cartilage from the healthy cartilage while preserving as much healthy tissue as possible (Ogilvie-Harris and Fitsialos, 1991; Moseley et al., 1996). Either a mechanical shaver or radiofrequency energy (RFE) device can be used during the debridement procedure. The RFE device was developed because using a mechanical shaver creates irregularities in the cartilage surface following the procedure and damages healthy adjacent cartilage and the surface of the articular cartilage (Barber et al., 2002). The RFE device uses heat to smooth the surface and is thought to be able to seal the surface of the cartilage (Barber et al., 2002). While the RFE device has been shown to be more accurate and create a smoother surface than the mechanical shaver, the heat from the RFE device causes chondrocyte death and there is some controversy over whether there is an advantage to using the RFE device over the mechanical shaver (Lu et al., 2001; Edwards et al., 2007). While several types of devices have been developed for use in human medicine, determining the appropriate settings and patterns to use on equine articular cartilage still

needs to be further researched in order for treatment with the RFE device to be a safe and effective procedure for use in equine medicine (Edwards et al., 2007). The end product of debridement is a smoother surface of articular cartilage that should be free of debris and inflammatory molecules (Cameron-Donaldson et al., 2004).

Abrasion Arthroplasty and Microfracture

Abrasion arthroplasty and microfracture are two different forms of bone-marrow stimulating procedures that are used to correct cartilage defects (Reinold et al., 2006). The purpose of these procedures is to access the bone marrow and allow the bone marrow to exude out of the bone and fill the cartilage defect (Steadman et al., 2001). Once the clot forms within the defect, mesenchymal cells within the bone marrow are able to differentiate into fibrochondrocytes and create a fibrocartilagenous repair tissue that covers the lesion (Ogilvie-Harris and Fitsialos, 1991; Reinold et al., 2006).

In abrasion arthroplasty procedures, the surgeon uses a mechanical shaver or burr to remove degenerative tissue and abrade the subchondral bone of the lesion to access the marrow beneath the surface of the bone (Ogilvie-Harris and Fitsialos, 1991; Reinold et al., 2006). The microfracture procedure is also the same for horses and humans (Frisbie et al., 1999). During the procedure, the surgeon debrides all of the unstable cartilage from the exposed bone and creates a rim of healthy cartilage around the defect that will allow the marrow clot to pool as it forms. An arthroscopic awl is used to make many holes approximately 3-4 mm apart. The holes are placed as close as possible together without breaking into each other. This maintains the integrity of the subchondral plate and the joint surface shape while providing a surface for the clot to adhere. The marrow

flows over the lesion and forms a marrow-rich clot. Complications of the procedure include transient pain and a catching or locking event during joint motion (Steadman et al., 2001).

Microfracture has been shown to successfully create repair tissue in the defect and human patients report decreased pain and improved function following surgery (Vachon et al., 1986; Steadman et al., 2003). In both horses and humans, the microfracture procedure has been shown to improve function and promote development of cartilaginous tissue containing type II collagen within the lesion (Frisbie et al., 1999; Bae et al., 2006). After rehabilitation, microfracture has been shown to improve function in 95% of patients when evaluated with questionnaires 7-17 years post-operation (Steadman et al., 2003). Therefore, microfracture may be a good long-term solution to articular cartilage defects in both species.

Autologous Chondrocyte Implantation

Autologous chondrocyte implantation (ACI) involves the placement of chondrocytes into a cartilage defect to try to promote the production of articular cartilage repair tissue (Hambly et al., 2006). There are currently three generations of ACI available to patients. The first case of ACI in humans was reported by Brittberg et al. in 1994. The first generation surgery consists of two procedures. The first involves obtaining an arthroscopic biopsy of healthy cartilage from a non-weight bearing surface of the knee joint. The cartilage is then cultured in vitro for 11-21 days. In the second phase of the surgery, a periosteal flap is taken from bone near the articulating surface of the joint and is sutured over the cartilage lesion (Brittberg et al., 1994). After periosteal

fixation, the graft is tested for water-tightness and is then sealed with a fibrin glue prior to injection of the chondrocytes beneath the periosteum (Minas and Peterson, 1999).

A major complication associated with the first generation of ACI is hypertrophy of the periosteal patch. During hypertrophy, the patch pulls back from the edges of the rim of the defect and new lesions may form (Peterson et al., 2000, Micheli et al., 2001; Hambly et al., 2006). The second generation of ACI addresses this issue through use of a biomaterial with a collagen membrane in place of the periosteal flap. The use of the second generation technique decreases the incidence of complications related to post-operative hypertrophy (Haddo et al., 2004; Hambly et al., 2006).

Matrix-induced ACI (MACI), the third generation of ACI, is the latest technique that has been developed by surgeons and researchers (Ebert et al., 2008). This procedure utilizes a biomaterial that has a scaffold for cell growth and contains cultured chondrocytes which can generate new articular tissue (Hambly et al., 2006). During the first procedure, chondrocytes are taken from the cartilage, cultured, and are used to seed a collagen membrane (Ebert et al., 2008). The defect is debrided and all damaged cartilage is removed down to the subchondral plate to create a circular area to fit the graft. The scaffold is cut to fit the defect and after debridement the material is placed directly onto the defect in layers (Marcacci et al., 2002). Fibrin glue is then used to fix the graft in place (Marcacci et al., 2002; Hambly et al., 2006; Ebert et al., 2008). The third generation ACI procedure decreases the risks associated with the ACI surgery because arthroscopy can be used instead of arthrotomy (Marcacci et al., 2002).

The ACI procedure for horses is very similar to the procedure utilized in human medicine and can include use of either a periosteal flap or a chondrocyte-seeded matrix

(Barnewitz et al., 2006; Nixon et al., 2011). The surgical procedure is usually followed with an initial mild lameness which does not cause any additional health issues. The lameness improves and disappears throughout the rehabilitation program as the horse is exercised (Frisbie et al., 2009). In a 12-month study, a cartilage seeded matrix and a periosteal graft performed similarly and the repair tissue within the joints was shown to increase throughout the study following either type of procedure (Frisbie et al., 2009). Since ACI has been shown to be effective at treating lesions exceeding 6 cm^2, it presents itself as a strong option for treating horses with larger cartilage defects (Brittberg et al., 1994).

Autologous Osteochondral Mosaicplasty

The autologous osteochondral mosaicplasty (OATS) procedure can be done arthroscopically or via arthrotomy depending on the location of the defect and access to the site. In this surgery, multiple circular grafts are taken from non-weight-bearing surfaces of the joint and are delivered to the recipient site in the same procedure (Hangody et al., 2004). Multiple smaller grafts are used to avoid incongruity between the surface level of the graft and the surrounding articular cartilage (Yamashita et al., 1985). The use of grafts of varying sizes allows for a 70-100% defect-filling rate depending on the shape of the defect, the availability of articular cartilage in the donor sites, and the size of the plugs used (Hangody et al., 2004). It should be noted that while smaller plugs do improve joint surface congruity, larger sized grafts have improved fixation strength and are able to sustain greater forces prior to failure. This may have implications during the rehabilitation process (Duchow et al., 2000).

In the OATS procedure for both humans and horses, the surgeon first abrades the defect down to the subchondral bone and debrides the edges of the defect to healthy hyaline cartilage. The number and size of the grafts needed to fill the recipient site are determined by tapping a drill-guide into the subchondral bone. The location of the donor site varies based on the joint that is being operated on and the surgical procedure. In the knee, grafts are taken from the peripheral edges of the femoral condyles in an arthrotomy procedure and from the medial border of the medial femoral condyle in an arthroscopic procedure. A tubular chisel is tapped perpendicularly into the donor site to harvest the graft. After the graft is harvested, a recipient tunnel is created in the defect to match the size of the graft. The graft is then inserted perpendicularly to ensure that the graft is flush with the healthy hyaline cartilage surrounding the defect (Hangody et al., 2004). This process is repeated until the defect is filled, with the goal of making the articular surface as smooth as possible with proper fixation of the grafts (Yamashita et al., 1985).

Summary

- Surgical procedures for articular cartilage repair utilized in human and equine medicine share many similarities (Frisbie et al., 1999; Barnewitz et al., 2006).
- While microfracture is the most common articular cartilage repair procedure, the technique used depends on the size and characteristics of the defects (Brophy et al., 2009)
- Controversy exists regarding the efficacy of mechanical and EMF debridement and lavage of the articular cartilage as a treatment for articular cartilage defects (Lu et al., 2001; Edwards et al., 2007).

- Microfracture and ACI have been shown to be effective treatments in both human and equine models (Steadman et al., 2003; Frisbie et al., 2009).

Chapter 3

Rehabilitation

The goals for the period following surgery are to enhance chondrocyte regeneration, prevent articular adhesions, improve muscle tone, and prevent degeneration of the articular cartilage (Minas and Peterson, 1999). There are many suggested timetables available for human rehabilitation programming based on the surgical procedure (Table 1). These timetables vary based on the practitioner or researcher's opinions and experience (Marcacci et al., 2002; Hambly et al., 2006; Kreuz et al., 2007; Della Villa et al., 2010; Ebert et al., 2008). While timetables vary, the goals of rehabilitation are the same: to return the patient to full function and range of motion as quickly as possible without damaging the surgical site (Hambly et al., 2006). Continuous passive motion (CPM) and a gradual return to full weight bearing are the hallmarks of rehabilitation programs (Steadman et al., 2001; Steadman et al., 2007; Della Villa et al., 2010).

Surgical Technique		Initial Weight bearing (>20% of BW)	Time at Full Weight bearing	Initial ROM	Time when Full ROM Reached	Full Function Achieved
Debridement		Immediately	1-2 weeks	Full ROM Allowed	2-3 weeks	5 months
Marrow-Stimulating Procedures	Weight-bearing surface	6-8 weeks	8 weeks	30-70°	8 weeks	4-8 months
	Non-weight bearing surface	1-2 weeks	1-2 weeks	0-20°	After 8 weeks	4-8 months
ACI	Conventional	4-5 weeks	7-12 weeks	0-40°	12 weeks	12 months
	Accelerated	2 weeks	8 weeks	0-40°	12 weeks	12 months
OATS		6 weeks	8-10 weeks	0-60°	8-10 weeks	12-18 months

Table 1. Human rehabilitation timeline for each surgical technique (Steadman et al., 2001; Frisbie et al., 2003; Steadman et al., 2003; Reinold et al., 2006; Kreuz et al., 2007; Steadman et al.,. 2007; Ebert et al., 2008; Bedi et al., 2010; Della Villa et al., 2010; Ebert et al., 2010).

One of the difficulties of developing a rehabilitation program is the inability to assess graft maturation post-surgery (Elder et al., 2000). Mechanical forces caused by joint movement and weight bearing are thought to increase cellular differentiation of stem cells to chondrocytes, so the goal of the rehabilitation process is to create a progressive framework in which the person can return to full function as quickly as possible without damaging the integrity of the repair (Elder et al., 2000). There are many factors that should play a role in the decision making process while developing a rehabilitation program. The characteristics of the cartilage defect, the patient's age, health, and previous activity level, and the surgery repair procedure utilized should all be considered (Reinold et al., 2006).

Research with human athletes has shown that moderate activity levels should be continued 2-3 years after the initial rehabilitation program to improve the final outcome and return to sport following operation. This is due to both the positive effects of exercise on chondral regeneration in the knee and the improved strength and adaptation of the other components of the knee joint to physical stress (Kreuz et al., 2007). In the equine, post-operative exercise has been shown to increase the thickness of the repair tissue and the differentiation of fibrocartilage to hyaline-like cartilage (French et al., 1989). Dogs exposed to exercise were shown to have increased stiffness and thickness of articular cartilage due to increases in glycosaminoglycan content in the areas of the knee bearing the highest load during exercise (Jurvelin et al., 1986; Kiviranta et al., 1988). These benefits suggest a need to develop the rehabilitation program around mechanical stimulation of the cartilage.

While research supports the use of mechanical stimulation and suggests avoiding full weight bearing immediately following surgery, rehabilitation protocols for horses after articular cartilage defect treatment often call for stall rest for up to 8 weeks. During this period, the horse's movement is limited to shifting its weight and walking around its stall or small enclosed area (Frisbie et al., 2007; Fortier et al., 2010; McIlwraith et al., 2011). During this time, the horse is exposed to full weight bearing. Since constant pressure or lack of movement have been shown to cause degradation of the articular cartilage surrounding the point of pressure, the development of new methods of rehabilitation in the horse may greatly benefit rehabilitation time and the chances of returning to full function following surgery (Hall, 1963; Haapala et al., 2000).

Continuous Passive Motion

One of the central focuses of any human rehabilitation program is the use of CPM following the surgical procedure on a weight-bearing surface (Reinold et al., 2006; Bedi et al., 2010; Wilk et al., 2010). Immobilization causes flattening of the contact surface and degeneration of the articular cartilage (Hall, 1963). Lack of movement also leads to softening of the cartilage surface and decreased compressive stiffness. These characteristics have been attributed to the loss of proteoglycan content following immobilization (Haapala et al., 2000).

The positive effects of joint mobilization following surgery include mechanical stimulation of matrix production by the chondrocytes and increased nutrient delivery to the cartilage (Amiel et al., 1986; Mow and Huiskes, 2005). Synovial fluid has been shown to be crucial in delivering nutrients to the diarthrodial joint (Amiel et al., 1986). As the joint moves, compression of the articular cartilage causes a change in pressure which moves synovial fluid through the cartilage (Mow et al., 1980). The pathway through which mechanical stimulation leads to increased matrix production by the chondrocytes is unknown, but there has been an association between CPM and increased cartilage development in mammalian models (Williams et al., 1994; Mussa et al., 1999; Mow and Huiskes, 2005). A guinea pig model has shown that CPM for 7 hours per day for 5 days significantly increased the condylar cartilage thickness compared to the condylar cartilage found in the control animals that were restrained or allowed normal cage activity (Mussa et al., 1999). A different study showed that rabbits exposed to 2 days of intermittent active motion followed by 19 days of CPM showed increased replenishment of proteoglycans which aided in maintaining the cartilage structure

following proteolytically induced degradation of the proteoglycans in the matrix (Williams et al., 1994).

For these reasons, CPM is started within 6-24 hours following arthroscopic treatment in humans (Marcacci et al., 2002; Reinold et al., 2006; Della Villa et al., 2010). CPM allows for joint movement without weight bearing and provides mechanical stimulation without putting excess stress on the defect site. CPM is typically performed for 6-12 hours a day following treatments such as microfracture, autologous osteochondral mosaicplasty, and autologous chondrocyte implantation (Steadman et al., 2001; Hangody et al., 2004; Della Villa et al., 2010). CPM treatment continues until the full ROM is reached and the patient has reached full weight bearing capacity and is able to start walking and participating in low-impact sports (Reinold et al., 2006).

Passive ROM exercises can also be performed in the horse and involve the therapist picking up and stabilizing the horse's leg while moving the leg slowly through the ROM. Typically the therapist moves the horse's joint through its ROM for 10 repetitions at a time (Porter, 2005). However, the labor associated with this form of CPM and the potential of damage due to a horse resisting the treatment make CPM impractical. Instead, current rehabilitation protocols use hand-walking as a method of stimulating cartilage regeneration (Todhunter et al., 1993). This creates the need to come up with an alternative method of mechanical stimulation of the joint while minimizing weightbearing.

Cryotherapy

In addition to CPM, rehabilitation protocols often call for cryotherapy three times per day for 20 minutes. Cryotherapy aids in the acute phase of rehabilitation because it lowers the intra-articular temperature of the joint, decreases swelling, and may partially alleviate pain and discomfort following surgery (Hecht et al., 1983; Sánchez-Inchausti et al., 2005). However, cryotherapy has its limits and may even impede the rehabilitation process following the acute phase of rehabilitation. Cryotherapy has been shown to increase joint stiffness and decrease the patient's ability to sense the position of their joint. When exercise is expected immediately following cryotherapy treatment, the patient may be unable to control their ROM and may put excess weight on the joint due to the lessened pain response (Uchio et al., 2003). Therefore, therapists may want to only use cryotherapy during the early stages of rehabilitation right after surgery or during periods of time when the patient will not be asked to perform ROM or weight bearing exercises (Uchio et al., 2003).

Aquatic Therapy

Aquatic therapy has been shown to decrease pain and stiffness and increase physical function and strength of patients with osteoarthritic hips or knees (Hinman et al., 2007). In humans, patients undergoing hydrotherapy reported a significant decline in pain following the exercise sessions. These patients also exhibited increased walking speed and distance when compared to a control group, indicating an increase in muscle strength around the joint and improved joints stability (Foley et al., 2003). When compared to patients exercising on land, patients in a hydrotherapy exercise program experience significantly reduced pain before and after exercise (Silva et al., 2008).

The integration of aquatic therapy into equine rehabilitation programs following surgery may improve return to normal function by reducing stress on the injured limb and allowing for increased ROM while decreasing the force of weight on the treated defect (King et al., 2013). It is not recommended that horses be introduced to fluid levels that require swimming to stay afloat because this causes fatigue, stress, and may damage treated areas (McClintock et al., 1987). Fluid levels to the point of shoulder decrease effective body weight by 30% and levels up to the tubera coxae decrease effective body weight by 75% (McClintock et al., 1987). Underwater treadmills offer a high degree of customizability to a rehabilitation program, as the speed and water depth within the treadmill can be changed to gradually re-introduce the horse to full weight-bearing exercise and to increase muscle recruitment (Porter, 2005). Despite the potential for improved return to function, there have been little to no objective or conclusive studies regarding the impact of aquatic therapy on osteoarthritis progression and symptoms in the horse (Buchner and Schildboeck, 2006; King et al., 2013).

Another interesting component of aquatic therapy is the ability to alter the temperature of the water to change blood flow throughout the body. Changes in temperature may aid in reducing edema within the joint (Yamazaik et al., 2000). Changes in water temperature have been shown to affect peripheral resistance, with cooler water (32°C) causing vasoconstriction and warmer water (36°C) causing vasodilation (Yamazaki et al., 2000). Reduced weight bearing, edema, and joint stiffness through the use of aquatic therapy may be beneficial to equine rehabilitation procedures, but well-developed, objective research needs to be conducted to obtain a better understanding of how aquatic therapy can influence a horse's return to function following

surgical procedures of the articular cartilage (King et al., 2013). If aquatic therapy proves to be an effective method of rehabilitation after articular cartilage surgery it can be incorporated into the equine rehabilitation program as soon as any open wounds or surgical sites on the horse close (King et al., 2013).

Rehabilitation following Debridement

As stated above, the debridement surgical procedure merely removes any loose debris or inflammatory molecules (Cameron-Donaldson et al., 2004). The focus of the rehabilitation program for debridement is to maintain articular cartilage volume after removal of the articular surface and to obtain normal joint ROM as soon as possible. The rehabilitation process for debridement is much faster than in other procedures (Reinold et al., 2006; Steadman et al., 2007). During the first 1-2 weeks following surgery the patient is permitted to bear weight as tolerated but is given crutches to use for support (Steadman et al., 2007). Progressive ROM exercises begin immediately following the debridement procedure with no limits on the motion available to the patient (Reinold et al., 2006). Initially the exercises are non-weight bearing but by the end of the first week strengthening exercises and bicycles are permitted. Typically, full ROM is achieved by 2-3 weeks after surgery (Reinold et al., 2006). Depending on the location and size of the debridement, the patient typically begins walking on a treadmill around 6 weeks post-operation and progresses to exercises such as running by 4 months after surgery and skiing and tennis five months after surgery (Steadman et al., 2007). While this rehabilitation program is fairly rapid, progress from one stage to the next is still limited by pain symptoms or degenerative changes (Reinold et al., 2006). Debridement provides

a method of improving the articular cartilage surface and matrix environment without introducing new tissue to the area to correct the defect (Cameron-Donaldson et al., 2004).

Rehabilitation following Abrasion Arthroplasty and Microfracture

The purpose of rehabilitation following marrow-stimulating procedures such as microfracture and abrasion arthroplasty are to provide an environment that will encourage the differentiation of mesenchymal stem cells to articular cartilage-like cells that will create a repair cartilage (Steadman et al., 2001). A study of cartilage in an equine model showed that Type II collagen mRNA expression begins at 4-6 weeks following microfracture surgery and increases as the rehabilitation program progresses. By 8 weeks post-operation type II collagen, hyaline-like cartilage tissue, and proteoglycan aggregates were identified throughout all layers of tissue and in more than 2/3 of tissue secretions (Frisbie et al., 2003).

The rehabilitation time following microfracture treatment varies immensely based on the anatomic location and size of the defect (Steadman et al., 2001). Patients with lesions on weight bearing surfaces typically have a longer rehabilitation time and must remain non-weight bearing for a longer duration than patients with lesions on non-weight bearing surfaces (Bedi et al., 2010). For patients with treated lesions on a non-weightbearing surface, partial weight bearing is permitted immediately following surgery and full weight bearing is usually achieved 2 weeks following surgery, but the patient is constrained to a very small ROM (0-20°) for at least 8 weeks to avoid shear force on the marrow clot. After 8 weeks, the brace is gradually opened up at a rate which the patient

is able to tolerate without pain. ROM is gradually increased until reaching the limits of the brace and the brace is discontinued (Steadman et al., 2003).

For patients with a lesion on the weight bearing surfaces of the knee, the initial allowed ROM is much greater (0-60°), but the patient is restricted to crutch-assisted touchdown weight bearing for 6-8 weeks following surgery (Steadman et al., 2003; Bedi et al., 2010). Full weight bearing is permitted as tolerated by the patient starting at 8 weeks after surgery (Steadman et al., 2003). In both rehabilitation programs, the ROM and weight bearing are gradually increased, and patients typically see a faster return to sport than those who have gone through ACI or OATS procedures (Steadman et al., 2001; Marcacci et al., 2002; Reinold et al., 2006; Kreuz et al., 2007). Patients with lesions on weight-bearing surfaces typically return to pivoting and high-impact sports 4-6 months following surgery (Steadman et al., 2001).

Rehabilitation in horses following microfracture procedure is very different than rehabilitation programs in humans. Whereas human rehabilitation protocols stress minimizing weight bearing and utilizing CPM to stimulate differentiation to articular-cartilage-like cells, equine rehabilitation programs begin full weight bearing and limit movement immediately following surgery (Frisbie et al., 1999; Steadman et al., 2001). Following microfracture, horses are put on stall rest for 8 weeks. After this time, horses are walked for 5 min/day and the duration of the walks are increased by 5 min/week through week 12. At this time, trotting exercise begins on a treadmill, with two minutes of trotting being permitted during week 13, 5 minutes from weeks 14-17, 8 minutes from weeks 18-19 and 10 minutes from weeks 20-31. Galloping exercise then begins with 2 minute trot-gallop-trot intervals until postoperative month 12 (Frisbie et al., 1999).

Horses that went through this rehabilitation programs had defects that were 74% filled with repair tissue after a 12 month period, compared to horses who were not treated with microfracture and had only 45% of the defect filled with repair tissue (Frisbie et al., 1999). Measurements of Type II collagen in the carpus of these horses showed that 55% of the collagen was of Type II in the microfracture-treated group and only 25% of the collagen was Type II in the control group (Frisbie et al., 1999). This suggests that the rehabilitation program that was utilized in horses was successful in stimulating the production of articular cartilage-like tissue.

Rehabilitation following Autologous Chondrocyte Implantation

Research in humans has shown that the operated limb should be rested and elevated for the first 12-24 hours following ACI surgery (Kreuz et al., 2007; Ebert et al., 2008; Della Villa et al., 2010). After this period of rest, CPM is started immediately and patients perform 5-8 hours of CPM per day. Recommended angles of CPM usually range from 0˚ to 30˚ or 40˚ (Marcacci et al., 2002; Ebert et al., 2008; Della Villa et al., 2010).

The timeline of return to weight bearing is controversial. It is believed that the development of more advanced techniques such as MACI may allow patients to return to full weight bearing at a more rapid pace than conventional rehabilitation programs outline (Ebert et al., 2008; Ebert et al., 2010). Conventional rehabilitation programs keep the patient bearing less than 20% of their body weight through the use of crutches and strictly foot touch weight bearing for the first 4-5 weeks post-surgery and do not allow for return to full weight-bearing until 7-12 weeks post-surgery (Marcacci et al., 2002; Hambly et al., 2006; Kreuz et al., 2007; Ebert et al., 2008; Della Villa et al., 2010). However, recent

research has suggested that an accelerated protocol in which weight bearing is incrementally increased starting at 2 weeks post-surgery and full weight bearing is reached by 8 weeks after surgery does not cause detachment of the graft from the surgical site. This accelerated protocol may also increase mobility of the patient and decrease pain symptoms (Ebert et al., 2008; Ebert et al., 2010). Around 4 months after surgery, the patient is allowed to begin low-impact sports like running on grass. As time progresses, the patient can move to activities involving increased impact and turning (Kreuz et al., 2007). Return to high-contact sports involving cutting motions should be avoided for 12 months after surgery (Marcacci et al., 2002).

As in human medicine, rehabilitation protocols for horses following ACI vary depending on the researchers and practitioners designing the study. The general format of transitioning from surgery to exercise involves stall rest followed by a gradual introduction to extended periods of walking before introducing trot and gallop work (Frisbie et al., 2007). Horses are put on stall rest for 3 to 5 weeks post-surgery. Following this rest period and removal of sutures, horses are hand walked for five minutes a day, increasing the work by 5 minutes per week until the horse is walking for 20-30 minutes (Frisbie et al., 2007; McIlwraith et al., 2011). At this time, the horse can start trotting on a treadmill or in hand for 2 minute intervals. By four months post-operation, the horse performs two minute trot-gallop-trot intervals (Frisbie et al., 2007; McIlwraith et al., 2011). Some studies allow for turnout to small paddocks to graze for the entire day following the initial stall rest period (Barnewitz et al., 2006).

Despite the contraindications of return to full weight-bearing immediately post-surgery and the lack of CPM and ROM exercises, ACI procedures have been reasonably

successful in horses. In a study of eight horses, analysis of the cartilage 12 months after surgery showed repair tissue covering cartilage lesions, no abnormalities of the lesions, even distribution of cells throughout the repair tissue, and good integration between the graft and the surrounding articular cartilage and subchondral bone. There was a smooth transition from the repair tissue to the surrounding articular cartilage without any incidences of transplant detachment (Barnewitz et al., 2006). This indicates that the ACI procedure can be very successful in horses, and utilizing new modalities may open up further opportunities for a more rapid return to full function.

Rehabilitation following Autologous Osteochondral Mosaicplasty

The goal of rehabilitation following the OATS procedure is to avoid disruption of the transplanted bone plugs. The pace of the rehabilitation program is changed based on the size of the lesion and the number of bone plugs used during the surgery (Reinold et al., 2006). Patients begin a CPM program for 8-12 hours per day. The initial ROM is 0-60°, with 5-10° added to the ROM each day. Gentle weight bearing is allowed after week 6, and by weeks 8-10 full ROM and weight bearing are usually achieved. The return to sports is slower with the OATS procedure than with ACI. Typically patients can return to low-impact sports such as jogging 6-8 months following their procedure, but must avoid high-impact sports such as tennis, soccer, and basketball for 12-18 months post-surgery (Reinold et al., 2006).

The OATS procedure has been very successful in returning human and equine patients to their level of activity prior to injury (Hurtig et al., 2001; Gudas et al., 2005). One study compared the ability of athletes to return to their sport following microfracture

and OATS procedures. In this study, 93% of the patients who underwent the OATS procedure and 52% of the patients who underwent the microfracture procedure were able to return to their sport at the same level as they played at prior to their injury (Gudas et al., 2005). A study of the post-operative symptoms of horses following the OATS procedure showed that horses also respond well to this technique. In this procedure, horses were hand-walked for 20 minutes twice a day and performed lameness tests on a daily basis by trotting on a hard surface. Turnout was allowed after two weeks and after three months the horses began trotting for 20 minutes three times a week. By 3 weeks after surgery, none of the horses in the study were lame and observation of the osteochondral grafts 9 months after transplantation showed no degenerative changes. However, upon arthroscopic examination of the repair site it was easy to distinguish the repair tissue from the surrounding cartilage. While this rehabilitation program was successful in returning the horse to exercise while maintaining the integrity of the grafts, a more structured program may be beneficial in improving the quality of the repair tissue (Hurtig et al., 2001).

Summary

- Continuous passive motion is used to stimulate matrix production by chondrocytes and to avoid the deleterious effects of immobilization on the articular cartilage (Hall, 1963; Amiel et al., 1986; Mow and Huiskes, 2005). However, CPM is not feasible for use in equine rehabilitation (Todhunter et al., 1993).

- The use of aquatic therapy may be a solution to minimizing weight bearing during exercise in equine rehabilitation programs (King et al., 2013).
- The rehabilitation programs for humans with repairs on weight-bearing surfaces involve continuous passive motion and restricted weight bearing following surgery (Reinold et al., 2006).
- Rehabilitation programs for humans on non-weight bearing surfaces allows for return to weight bearing sooner but the range of motion is reduced to avoid shear forces on the repair site (Steadman et al., 2003).
- Rehabilitation programs for horses involve a period of stall rest followed by a gradual return to work (Hurtig et al., 2001).

Conclusion

In conclusion, human models of articular cartilage repair offer the equine industry an opportunity to identify the results of research that have been published and to adapt the results of this research to improve the quality of the equine rehabilitation process. Removing weight from the injured limb and utilizing CPM exercises following surgery aren't very realistic for treatment of the equine. However, the use of underwater treadmills and aquatic therapy may improve the repair cartilage development by stimulating the chondrocytes and reducing the effective weight of the horse's body on the joint while the horse exercises. Further research needs to be conducted to evaluate the benefits of these exercises on the development of healthy repair tissue in the joint and the athlete's return to sport. As research continues to eliminate the characteristics and needs of articular cartilage following surgery, it will be easier to adapt techniques in human medicine to appropriately fit equine rehabilitation science.

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