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MUSCLE DISORDERS: UNTYING THE KNOTS THROUGH NUTRITION

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Some unfortunate horses develop stiffness, painful muscle contractures, profuse sweating, and elevated respiratory rates during or following exercise. The term "tying-up" is used to describe horses with these clinical signs. In severe cases, horses may be unable to move their hindquarters after exercise, and muscle breakdown results in dark urine due to the release of myoglobin. Horses may be so painful with tying-up that they will paw and roll resembling colic. Other terms for this syndrome include azoturia, Monday morning disease, exertional rhabdomyolysis, and chronic intermittent rhabdomyolysis. It has been implied or assumed that there is one underlying cause for tying-up in horses. In 1917, Dr. Steffin commented on tying-up, saying "no one disease in the horse has been subject to so many theories and hypothetical suggestions as this one." This statement remains true. Veterinarians and owners have noted improvement in their horses' signs of tying-up with various new diets or supplements. The variable response of horses to these treatments has fueled the controversy regarding tying-up and its actual basis. In this article, we provide a brief review of the history of tying-up with regard to a nutritional basis and a summary of some of the most recent advances with regard to nutritional management of this syndrome.

A Search for a Nutritional Basis for Tying-Up

Tying-up was first described in draft horses during the preceding century. When some horses were rested from routine work on Sunday and fed their usual grain ration, they developed signs of tying-up on Monday morning when they resumed their work. A study performed in 1932 showed that draft horses given high amounts of nonstructural carbohydrates such as molasses were more likely to develop muscle damage with exercise (Carlstrom, 1932). As a result it became common to recommend a low-grain diet for all horses with tying-up. Carlstrom believed that the high-carbohydrate diet given while horses were resting resulted in loading of muscle glycogen that in turn precipitated lactic acid accumulation during exercise. While decreasing grain appears helpful for many horses with tying-up, this mechanism for rhabdomyolysis has never been substantiated. In fact, most horses tie-up when exercising at slow speeds when lactic acid is not produced (MacLeay

et al., 2000). There are no clearly documented cases of horses that develop severe lactic acid accumulation with tying-up following exercise.

As the automobile replaced the draft horse for transportation, race and pleasure horses became increasingly popular. Veterinarians began to note a milder syndrome of tying-up in these lighter breeds of horses. It was suggested that, similar to other species, a dietary vitamin E and selenium deficiency might cause muscle damage in tying-up horses. Vitamin E and selenium act to protect muscles from toxic products called oxygen free radicals that can be generated with exercise. Documented cases of a selenium-responsive muscle disease were reported in foals from several countries with low selenium soil content in the 1970s. The association with muscle disease led to the recommendation that horses with tying-up should be given a selenium and vitamin E supplement. When the selenium and vitamin E status was studied in tying-up horses, most adult horses had normal to high levels of selenium and vitamin E, likely because they were being supplemented in their diet (Roneus and Hakkarainen, 1985). Although selenium deficiency may not be the primary cause for tying-up, many practitioners report a decrease in the severity of tying-up when horses receive vitamin E and selenium supplementation. This may be due to the fact that horses generate more toxic free radicals with the tying-up syndrome and therefore have a greater need for supplementation.

A subsequent focus of investigation into tying-up was the role of an imbalance in dietary electrolytes (Harris and Snow, 1991). Electrolytes are body salts that maintain an electrical gradient across muscle cell membranes. During exercise, muscles contract when nerves stimulate a change in the electrical gradient and electrolytes move across the cell membrane. Muscle cells contain high concentrations of the electrolytes potassium and phosphate and low concentrations of sodium, chloride, and calcium. Electrolytes are obtained in the feed, and the concentrations in the body are regulated by uptake by the intestinal tract and elimination in sweat and urine. Endurance horses lose large amounts of fluids and electrolytes during competition, creating major electrolyte imbalances. Some of these horses may develop tying-up and exhaustion from dehydration, electrolyte losses, and high body temperatures. Endurance horses need to be on a daily electrolyte supplement and may need additional supplementation during endurance rides.

Subtle electrolyte imbalances are believed to have an important role in causing tying-up in some pleasure and racehorses. Studies by Harris and Snow (1991) in the United Kingdom have focused on determining electrolyte balance in horses with tying-up. Blood samples do not accurately reflect electrolyte balance in horses so a technique that checks the balance of salts between urine and blood was used to study tying-up. Commercial diets were found to be too low in salt (sodium chloride) and most horses needed an additional 1-2 ounces of salt to maintain proper balance. While some horses improved dramatically by adding electrolytes in the form of table salt (sodium chloride), lite salt (potassium chloride), or epsom salt (magnesium chloride), other horses showed no improvement.

Perhaps one of the major roadblocks in interpreting research into tying-up is the assumption that all horses that show evidence of muscle pain and cramping following exercise have the same disease. Many studies group a small number of horses of many breeds and athletic types together to find one unifying cause. As a result, a great deal of controversy and confusion has developed regarding the cause and approach to treatment of this condition. Tying-up or exertional rhabdomyolysis likely represents a description of several muscle diseases that have common clinical signs. By applying clinical protocols that include muscle biopsies and exercise testing, a number of specific disorders recently have been identified.

Classification of Tying-Up

Occasionally, horses diagnosed with tying-up actually have strained a specific muscle group. Tying-up from a clinical standpoint can be divided into two syndromes: 1) sporadic rhabdomyolysis following exercise in horses that have a previous history of satisfactory performance, or 2) chronic exertional rhabdomyolysis in horses with repeated episodes of tying-up from a young age.

Sporadic Tying-Up

LOCAL MUSCLE STRAIN

Local muscle strain is a common injury in performance horses. Several factors may predispose horses to muscle strains, such as an inadequate warm-up, pre-existing lameness, exercise to the point of fatigue, and insufficient training. Muscles over the back are frequently injured in jumpers, dressage, and harness horses. The hamstring muscles on the back of the rear limbs are more frequently damaged in working Quarter Horses. Affected muscles are painful upon deep palpation and may feel warm. In chronic cases, hardened areas within the muscle may represent fibrosis and ossification. The stride has a short anterior phase with a characteristic hoof-slapping gait.

CLINICAL SIGNS OF SPORADIC TYING-UP

More generalized muscle damage often results in overall muscle soreness, reluctance to move, sweating, and rapid respiratory rates. A diagnosis of sporadic tying-up is made on the basis of a horse with no previous signs of tying-up, signs of muscle cramping and stiffness following exercise, and moderate to marked elevations in blood markers for muscle damage such as creatine kinase (CK) and aspartate transaminase (AST). Horses with signs of tying-up should stop exercising and be moved to a well-bedded stall with access to fresh water. A veterinarian should be

called to assess whether horses need intravenous or oral fluids, tranquilizers, or pain relievers. Rest with a few minutes of hand walking once the initial stiffness has abated is of prime importance. The diet should be changed to good-quality hay with little grain supplementation, salt, and a vitamin/mineral mix. The amount of rest a horse should receive is controversial. Horses with chronic problems with tying-up appear to benefit from an early return to a regular exercise schedule. Horses that appear to have damaged their muscles from overexertion may benefit from a longer rest period with regular access to a paddock. Training should be resumed gradually and a regular exercise schedule, which will match the degree of exertion to the horses underlying state of training, should be established. Endurance horses should be encouraged to drink electrolyte-supplemented water during an endurance ride and monitored particularly closely during hot, humid conditions.

The most common cause of sporadic tying-up is exercise that exceeds the horse's underlying state of training. The incidence of muscle stiffness also has been observed to increase during an outbreak of respiratory disease. Deficiencies of sodium, calcium, vitamin E, and selenium in the diet may also contribute to muscle cell damage. Since the inciting cause is usually temporary, most horses respond to rest, a gradual increase in training, and diet adjustments. The ease of treating horses with overexertion may account for the myriad of treatments guaranteed to cure tying-up in horses. Skeletal muscle shows a remarkable ability to repair within 4-8 weeks following injury.

Chronic Exertional Rhabdomyolysis

A number of horses, predominantly fillies, will have recurrent episodes of rhabdomyolysis even with light exercise. Chronic exertional rhabdomyolysis is seen in many breeds of horses, including Quarter Horses, Paints, Appaloosas, Thoroughbreds, Arabians, Standardbreds, and Morgans. Several causes for chronic rhabdomyolysis have been proposed. These include electrolyte imbalances, hormonal imbalances, lactic acidosis, and vitamin E and selenium deficiencies. Many of these proposed causes do not have a sound scientific basis. As such we recommend that a complete battery of diagnostic tests be used to identify the cause of tying-up whenever possible.

Further diagnostic tests to try to determine the cause of chronic tying-up include a complete blood count, serum chemistry panel, blood vitamin E and selenium concentrations, urinalysis to determine electrolyte balance, exercise testing, muscle biopsy, and dietary analysis. A muscle biopsy may be useful in determining the basis for chronic rhabdomyolysis. Two forms of chronic tying-up have been identified using various forms of muscle biopsies. **Polysaccharide storage myopathy (PSSM)** is a form of tying-up in Quarter Horse-related breeds, warmbloods, and drafts. Biopsies of PSSM horses reveal many muscle fibers with

subsarcolemmal vacuoles, dark p-aminosalicylic acid (PAS) staining for glycogen, and most notably abnormal complex polysaccharide accumulation in muscle fibers (Valberg et al., 1992). **Recurrent exertional rhabdomyolysis (RER)** is a disorder of Thoroughbreds and likely Standardbred and Arabian horses. Muscle biopsies are characterized by numerous mature muscle fibers with centrally located nuclei and moderately dark PAS stains for muscle glycogen without any complex polysaccharide accumulation (Valberg et al., 1999a). In some horses, the specific cause of tying-up is not known at this time.

Recurrent Exertional Rhabdomyolysis

RER is most common in fit young fillies at the racetrack. It has a more equal sex distribution after four years of age and is found most commonly in horses with a nervous temperament (MacLeay et al., 1999a). Factors that trigger episodes of rhabdomyolysis include excitement with exercise, rest prior to exercise, galloping or breezing exercise, and any lameness even if it does not interrupt the exercise regime. Many fillies with tying-up are in intense training, have trouble maintaining body weight, and are therefore fed at least 12 lb of grain or more. The reason why certain horses are prone to tying-up and others that are managed identically are not may be related to inheritance. Studies of equine lymphocyte antigens provide support for a familial basis for RER in Standardbred horses (Collinder et al., 1997). Genetic studies in Thoroughbreds suggest that susceptibility is inherited as a dominant trait (MacLeay et al., 1999b). That is, if one parent had RER, there is a 50% chance of the foal being susceptible to RER no matter who the other parent is. Whether the offspring expresses the disease depends on the diet, management, and training regime. A diagnosis of RER is based on the history and clinical signs as well as documented elevations in muscle proteins (serum AST and CK) that leak into the bloodstream when muscle is damaged. Muscle biopsy findings in affected horses include varying stages of muscle necrosis and regeneration with centrally located myonuclei.

THE BIOCHEMICAL BASIS FOR RER

A specific cause for the form of tying-up in many Thoroughbreds has recently been identified. It appears that the mechanism by which muscle contraction is regulated can be disrupted by excitement and exercise in some susceptible horses (Lentz et al., 1999). This discovery was based on the observation that intercostal muscle biopsies from RER horses readily develop contractures when exposed to agents (halothane and caffeine) that increase intramuscular calcium release. The threshold for developing a contracture is much lower for RER horses compared to normal horses and is similar to a muscle disease in people and swine called malignant hyperthermia. Every time a muscle contracts, calcium is released from muscle

storage sites and then taken back up into storage sites for muscle relaxation. The altered contraction and relaxation of muscle suggests that abnormal intracellular calcium regulation is the cause of this form of RER. These intramuscular calcium concentrations are extremely small compared to the amount of calcium in the rest of the body and are completely independent of dietary calcium concentrations.

DIETARY MANAGEMENT OF RER

Obviously any diet for equine athletes needs to have a proper balance of vitamins, minerals, electrolytes, protein, fiber, and starch. Particular attention should be given to providing adequate electrolytes, vitamin E, and selenium. One of the problems with diets for nervous horses with RER in race training is that they often need to contain at least 28 MCal of digestible energy per day. To provide this energy, the starch content of the diet has traditionally been very high (>12 lb of grain/day) and this further exacerbates the excitability of the horse. Recent research suggests that replacing much of the grain in the diet with a fat supplement such as vegetable oil or rice bran is beneficial and will significantly decrease the amount of muscle damage. In a recent dietary trial, we exercised 5 Thoroughbred horses with RER on a treadmill for 5 days a week while they consumed hay and a variety of energy supplements for 3 weeks at a time. We found that keeping the caloric density at the calculated daily requirement of 21 MCal/day resulted in lower serum CK post exercise than when the amount of a corn/oat-based pellet was increased to provide 28 MCal/day (MacLeay et al., 2000). In contrast, if extra calories were provided with a fat supplement rather than a grain supplement at 28 MCal/day, no increase in post-exercise serum CK activity occurred. This research led to the development of a high-fiber, low-starch, high-fat diet called Re-Leve that is ideally suited to the management of RER in racehorses. No significant differences in muscle glycogen or lactate concentrations were apparent in our original studies as a result of feeding fat (MacLeay et al., 1999c). The effect of fat may lie in the ability to remove starch, which will decrease a key triggering factor for RER, excitability, in susceptible horses.

OTHER MANAGEMENT STRATEGIES FOR RER

Prevention of further episodes of RER in susceptible horses should also include standardized daily routines and an environment that minimizes excitement. The daily management of the horse including time of feeding, position in the stable, order of exercise, pasturemates, etc. should be evaluated to provide the lowest stress in the horse's day to day routine. The use of low doses of acepromazine before exercise is believed to help some excitable horses. Daily exercise is essential, whether in the form of turnout, longeing, or riding. In the past, horses have been box stall rested for several weeks following an episode of RER. It is the author's opinion that this is counterproductive and increases the likelihood that the horses

will develop RER when put back into training. The initial muscle pain usually subsides within 24 hours of acute RER, and daily turnout in a small paddock can be provided at this time. Subsequently, a gradual return to performance is recommended once serum CK is within normal range.

Dantrolene (2-4 mg/kg orally) given one hour before exercise may be effective in preventing RER in some horses. Dantrolene is used to prevent malignant hyperthermia in humans and swine by decreasing the release of calcium from the calcium release channel. Phenytoin (1.4-2.7 mg/kg orally twice a day) has also been advocated as a treatment for horses with RER (Beech et al., 1988). Therapeutic levels vary, so oral doses are adjusted by monitoring serum levels to achieve 8 ug/ml but not exceed 12 ug/ml. Phenytoin acts on a number of ion channels within muscle and nerves including sodium and calcium channels. Unfortunately, long-term treatment with dantrolene or phenytoin is expensive.

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Polysaccharide Storage Myopathy in Quarter Horses and Related Breeds

Polysaccharide storage myopathy (PSSM) has been identified in Quarter Horses, warmbloods, and draft horses (Valberg et al., 1992, 1997; Valentine et al., 1998). It is an uncommon occurrence in other equine breeds. The disease is characterized by the accumulation of phosphorylated glucose, glycogen, and abnormal polysaccharide in skeletal muscle.

CLINICAL SIGNS OF PSSM

Horses with PSSM often develop episodes of rhabdomyolysis at a young age when longed or broken to ride. Rest for a few days prior to exercise is a common triggering factor. Horses may have one episode per year or be affected at every exercise session. Episodes are characterized by a tucked-up abdomen, fasciculations, a camped-out stance, sweating, gait asymmetry, hind limb stiffness, and reluctance to move. Some horses paw or roll resembling colic. Myoglobinuria and recumbency occur occasionally with severe episodes. Serum CK and AST are increased during an episode (usually >10,000 U/L), and unlike other forms of rhabdomyolysis, subclinical episodes characterized by persistently abnormal CK are common (Valberg et al., 1997). Draft horses may be affected by a related disorder that has slightly different clinical signs. These include loss of muscle mass, difficulty standing with one hind leg raised, difficulty in backing without shaking a hind limb, progressive weakness, and recumbency. Elevations in CK and AST are often less than 10,000 U/L in drafts with this syndrome. Equine polysaccharide storage

myopathy (EPSM) has been used to characterize the draft syndrome (Valentine et al., 1998).

DIAGNOSIS OF PSSM

A definitive diagnosis of PSSM should be based on the presence of PAS positive inclusions in scattered fast twitch muscle fibers in a muscle biopsy. An open surgical biopsy to remove a 1.5"x 1.5"x 2" sample of the semimembranosus is readily performed in the field, and samples can be shipped chilled or on dry ice overnight to specialized laboratories (Valberg et al., 1997). PAS positive inclusions are readily distinguishable in frozen sections, and these samples can also be used for other biochemical assays, thereby making frozen tissue more useful than formalin-fixed muscle. Using the diagnostic criteria of abnormal PAS positive polysaccharide inclusions, PSSM is seen in particular Quarter Horse bloodlines, warmbloods, and draft horses. Pedigree analysis of Quarter Horses, Paints, and Appaloosas with PSSM supports a familial basis for this condition. Other laboratories have diagnosed PSSM solely on the basis of an apparent increase in muscle glycogen staining, and this has unfortunately resulted in the application of the term PSSM to a wide variety of breeds with various symptoms (Valentine et al., 1998). Complex polysaccharide is a rare finding in the Standardbred, Thoroughbred, Arabian, or other breeds of horses evaluated by our laboratory for exertional rhabdomyolysis.

PATHOPHYSIOLOGY

Because muscle glycogen concentrations in PSSM horses are 1.5 to 4 times those of normal horses or other breeds of horses with exertional rhabdomyolysis, this disorder is classified as a glycogen storage disease (Valberg et al., 1992). Glycogen storage diseases can result either from impaired utilization and breakdown of glycogen by tissues or increased and abnormal glycogen synthesis. No limitations in the ability of skeletal muscle to metabolize glycogen have been identified in PSSM horses. In fact, PSSM horses have higher glycogen utilization rates than healthy horses during anaerobic exercise (Valberg et al., 1999a). As such the metabolic defect responsible for marked glycogen accumulation appears to involve abnormal regulation of glycogen synthesis rather than a defect in utilization. We have found that horses with PSSM clear glucose from the bloodstream after an IV bolus or oral meal much faster than normal horses. It appears they do this because of increased insulin sensitivity (De La Corte et al., 1999a). When insulin is given to PSSM horses it causes a profound drop in blood sugar relative to normal horses which lasts for twice as long. Thus, it appears that one of the abnormalities in PSSM is that when fed a starch meal, these horses store a higher proportion of the absorbed glucose in their muscle compared to normal horses. The mechanism of glucose transport into muscles of PSSM does not appear to be regulated in the

same fashion as healthy horses. Why this in itself causes muscle cells to become damaged with exercise is not clear at this time. The specific inherited cause of PSSM in horses remains unknown. PSSM can naively be seen as the opposite of type 2 diabetes.

PREVENTION

Diet. The research performed by our group on PSSM would suggest that one of the ways to manage this condition is to decrease the amount of starch in the diet. In contrast to Thoroughbreds with RER, breeds of horses with this disorder are often very easy keepers and therefore do not need many additional calories over and above hay. In addition, horses with PSSM are rarely performing at exercise intensities and durations that require a high caloric input. We have found, however, that even a small amount of fat added to the hay ration can have a beneficial effect on decreasing muscle glycogen concentrations (De La Corte et al., 1999b). This effect is likely due to the ability of dietary fat to decrease blood glucose and insulin concentrations. Adding 2 lb of rice bran per day to grass hay resulted in a significant decrease in muscle glycogen and glucose 6 P concentrations in PSSM horses within 3 weeks. Feeding fat has been shown to decrease insulin-sensitive glucose transport in other animals, and this may be a further reason that fat supplementation is beneficial to PSSM horses.

The diet of PSSM horses is best adjusted to eliminate grain or sweet feed and provide a diet of roughage with a fat supplement. In our experience, rice bran is a convenient mechanism of providing fat. Fussy eaters, warmbloods in heavy training, and draft horses may benefit from Re-Leve, a very palatable high fat diet developed by Kentucky Equine Research. Corn oil on alfalfa pellets provides another fat source without having to feed grain but tends to be messy for owners to feed. Horses receiving corn oil should also receive a supplemental 600-1000 IU/day of vitamin E. Some veterinarians suggest that PSSM horses should be fed a diet consisting of 25% fat. It may be that draft breeds benefit from such high fat diets; however, in our experience it is difficult to reach these levels of dietary fat intake, and it is unnecessary in Quarter Horse-related breeds with PSSM.

Training. Horses with PSSM will not improve if the only change made is the addition of dietary fat (De La Corte et al., 1999b). Prevention of further episodes of rhabdomyolysis requires a very gradual increase in the amount of daily exercise horses experience. Minimizing stress and providing regular routines and daily exercise are highly beneficial. Turnout each day with other horses in as large an area as possible will keep the horse active and is the single most important thing that can benefit these horses in my experience. If there has been a recent severe episode of tying-up, I recommend turning the horse out for two weeks on the diet recommended above. After switching the horse's diet for two weeks, the horse can begin longeing once a day for five minutes at a walk and trot. Gradually

increase the time by two minutes a day. If the horse seems stiff, stand the horse for one minute and then see if the stiffness persists when walking. If stiffness is present, stop there; if not, continue after a two-minute walk. When the horse can trot 15 minutes, provide a five-minute break at a walk and gradually increase walking and trotting after this. Once the horse has reached 30 minutes of trotting on a longe line (with a break at 15 minutes), then begin to ride for 20 to 30 minutes and gradually increase the length and intensity of exercise. It should take at least three weeks of exercise before the horse is ridden. Keeping horses with PSSM fit increases oxidative metabolism and glycogen utilization, and this seems the best prevention against further episodes of tying-up.

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