Optimal function of skeletal muscle is essential for successful athletic performance. Even minor derangements in locomotor muscle function will impact power output, coordination, stamina and desire to work during exercise. While many myopathies are easy to recognize in the acute stages, low grade muscle strains or weakness and chronic myopathies may be difficult to diagnose. The challenges of identifying their contribution to poor performance in horses include;

1) differentiating between true pain with exercise and an uncooperative attitude
2) locating and assigning significance to focal muscle strain
3) determining the degree to which orthopedic pain contributes to muscle pain
4) determining the degree to which myopathies contribute to orthopedic pain
5) identifying muscle weakness as a component of gait alterations
6) differentiating myogenic from neurogenic weakness

Classification of Exertional Myopathies

Horses with exertional myopathies often fall into one of two main categories; 1) horses in which an intrinsic muscle defect does not appear to be present, but a temporary imbalance within the muscle cells causes a sporadic exertional myopathy and; 2) horses in which the primary underlying susceptibility appears to be the result of an intrinsic defect in the muscle resulting in a chronic exertional myopathy.

Chronic Exertional Myopathies

Known causes of chronic ER include recurrent exertional rhabdomyolysis, type 1 and type 1 PSSM and Malignant Hyperthermia. There may well be yet other unrecognized causes.

Recurrent Exertional Rhabdomyolysis (RER): RER refers to a subset of chronic exertional myopathies affecting approximately 5% of Thoroughbreds and Standardbreds. This is believed to be due to an abnormality in intracellular calcium regulation that is intermittently manifested during exercise. Although, several characteristics of RER muscle are very similar to those of humans and swine with malignant hyperthermia (MH), a defect in the ryanodine receptor associated with MH has not been identified in RER horses. At present the exact defect in intracellular calcium regulation with RER is not known. Mares more commonly show signs of RER than males, however, no general correlation has been observed between episodes of rhabdomyolysis and stages of the estrus cycle. Nervous horses (usually young fillies) have a higher incidence of rhabdomyolysis than calm horses. Horses on a high grain diet are more likely to show signs of RER, and one study found a higher prevalence of rhabdomyolysis among horses with lameness.
**Genetics:** A genetic susceptibility to RER appears to exist in Thoroughbred horses where RER-afflicted horses may pass the trait along to 50% or more of their offspring. Studies of Standardbred horses with RER suggest that there is potentially a heritable basis for this condition in this breed as well. There are anecdotal reports of higher prevalence of RER in certain Arabian horse families.

**Diagnosis:** A presumptive diagnosis of RER is based on clinical signs of muscle pain and the presence of risk factors commonly associated with RER. Skeletal muscle biopsies from Thoroughbred and Standardbred horses with active signs of RER often show an increased number of mature muscle fibers with centrally displaced nuclei, increased subsarcolemmal staining for glycogen, and a variable amount of muscle necrosis and regeneration. There is a notable absence of abnormal amylase-resistant polysaccharide in muscle biopsies from RER horses.

**Malignant Hyperthermia (MH):** MH is due to an autosomal dominant mutation in the skeletal muscle ryanodine receptor and is present in 1% or less of American Quarter Horses and Paints. Affected horses may intermittently show signs of tying up and high body temperatures. Some MH affected horses have died suddenly after an episode of tying up. The MH defect can co-exist with the GYS1 mutation for type 1 PSSM. The combination of these two mutations makes signs of tying-up more severe, increases recurrence of high serum CK and makes horses more resistant to improvement with changes in diet and exercise. In addition, horses with MH may develop classic signs under general anesthesia of excessive body temperature, rigor, metabolic acidosis and death. Genetic testing is recommended in Quarter Horse and Paint horses with difficult to manage forms of PSSM or a family history of post-anesthetic complications. Testing is available through the Veterinary Diagnostic Laboratory at the University of Minnesota [http://www.vdl.umn.edu/vdl/ourservices/neuromuscular.html](http://www.vdl.umn.edu/vdl/ourservices/neuromuscular.html) and University of California, Davis.

**Polysaccharide Storage Myopathy:** Several acronyms have been used for polysaccharide storage myopathy besides PSSM including EPSM and EPSSM and debate existed as to whether these acronyms encompassed one muscle condition. In 2008, the presence of amylase-resistant polysaccharide in skeletal muscle from Quarter Horses was found to be highly associated with a mutation in the glycogen synthase 1 gene (GYS1). Some cases previously diagnosed with PSSM by muscle biopsy, particularly those with amylase-sensitive glycogen, did not possess the genetic mutation suggesting that there are at least two forms of PSSM. For clarity, the form of PSSM caused by a GYS1 mutation is now termed **type 1 PSSM** whereas the form of PSSM that is not caused by the GYS1 mutation and whose origin is yet unknown is now termed **type 2 PSSM**.

**Type 1 PSSM:** The GYS1 mutation responsible for type 1 PSSM is present in over 20 different horse breeds. The highest prevalence of PSSM appears to occur in draft horses derived from Continental European breeds, in contrast, the prevalence of PSSM is very low prevalence in breeds such as Shires and Clydesdales. Prevalence in Quarter Horses range from 6 to 10% and 6 to 8% for American Paint and Appaloosa horses. The highest frequency of Type 1 PSSM occurs in halter Quarter Horses (28% affected) and the lowest frequency in racing Quarter Horses. The GYS1 mutation has been identified in approximately 72% of Quarter Horses diagnosed with PSSM by muscle biopsy and in 18% of Warmbloods of a variety of types diagnosed with PSSM.
by muscle biopsy. The prevalence of type 1 PSSM is very low in light horse breeds such as Arabians and Thoroughbreds.

Etiology: Glycogen is formed by the enzymes glycogen synthase and branching enzyme. The autosomal dominant GYS1 mutation produces a gene product, glycogen synthase, which has an arginine substitution for histidine at codon 309. The effect of this amino acid substitution is a higher than normal activity of glycogen synthase both at rest and when activated by glucose 6-phosphate. As a result, skeletal muscle of PSSM horses has 1.5 to 4 fold higher concentrations of glycogen than normal horse muscle. The accumulation of abnormal polysaccharide is in itself not the cause of muscle dysfunction in PSSM since foals as young as 1 month of age may show evidence of muscle damage prior to the formation of abnormal polysaccharide in skeletal muscle fibers. Rather, the persistent glycogen synthase activity in type 1 PSSM horse muscle appears to disturb the normal flux of muscle energy metabolism during exercise.

Acute clinical signs: Horses usually show signs of PSSM at an average 6 years of age, however, this can range from 1 to 14 years of age and some horses are asymptomatic. In general, owners describe horses with type 1 PSSM as having a calm and sedate demeanor. Acute clinical signs include tucking up of the abdomen, fasciculations in the flank, muscle stiffness, sweating reluctance to move forward and overt muscle contractures. The hindquarters are frequently most affected, but back muscles, abdomen, and forelimb muscles may also be involved. Signs of pain can last for more than 2 hours and about 10% of cases becoming recumbent. Muscle pain often occurs with less than 20 minutes of exercise at a walk and trot especially when horses are unfit at the commencement of training or after horses have had a substantial period of rest. A diet high in NSC exacerbates these signs. During an acute episode of ER, horses with type 1 PSSM often have markedly elevated serum CK activity of >35,000 U/L and myoglobinuria may be present. Severe colic-like pain post-exercise and myoglobinuric renal failure are less common presenting complaints. Some owners report a seasonal incidence to development of acute clinical signs which some have attributed to quality of grass available at the time.

Chronic clinical signs: Light breeds: In riding horses a lack of energy when under saddle, reluctance to move forward, stopping and stretching out as if to urinate and a sour attitude towards exercise occur. Horses may have a combination of low grade reluctance to exercise, poor performance and repeated episodes of ER. The range of severity of clinical signs of PSSM can be wide with some horses being asymptomatic and others completely incapacitated. Serum CK activities are often elevated in untreated Quarter Horses, even when horses are rested. While horses are symptomatic, CK will usually increase by 1000 U/L or more 4 hours after 15 minutes of exercise at a trot. The median CK and AST activity for all PSSM Quarter Horses with muscle biopsies submitted to the University of Minnesota was 2,809 and 1,792 U/L, respectively. Affected Quarter and Paint Horse foals and weanlings may develop rhabdomyolysis without exercise.

Draft Horse and Draft Crosses: The average age of draft horses diagnosed with PSSM is about eight years of age. Many draft horses with PSSM are asymptomatic. Signs of severe rhabdomyolysis and myoglobinuria may occur in horses fed high grain diets, exercised irregularly with little turn out or horses that undergo general anesthesia. Other signs of PSSM in draft horses include progressive weakness and muscle loss resulting in difficulty rising in horses.
with normal serum CK activity. Pronounced weakness is more prevalent in homozygotes for the
GYS1 mutation. Gait abnormalities, such as excessive limb flexion, fasciculations, and trembling
are also reported in draft horses. Although the condition Shivers was previously attributed to
PSSM, a recent study found no causal association between these two conditions. The median
serum CK and AST activities in draft horses from which biopsies were sent to the University of
Minnesota was 459 and 537 U/L, respectively.

Diagnosis: A genetic test for the GYS1 mutation can be performed on whole blood or hair root
samples in North America at the University of Minnesota (http://www.vdl.umn.edu/vdl/ourservices/neuromuscular.html) and in Europe by Laboklin (http://www.laboklin.co.uk/laboklin/GeneticDiseases.jsp). MH testing is provided at the
University of Minnesota and the University of California, Davis. Muscle biopsy can also
provide a means to diagnose type 1 PSSM. The distinctive features of type 1 PSSM in muscle
biopsy samples are numerous subsarcolemmal vacuoles and dense, crystalline periodic acid
Schiff’s (PAS) positive, amylase resistant inclusions in fast twitch fibers. Genetic testing
provides the gold standard for diagnosis because a false negative diagnosis of type 1 PSSM by
muscle biopsy may occur if biopsy samples are small or if horses are less than 1 year of age.

**Type 2 PSSM:** There is much less known about type 2 PSSM, because as it turns out, previous
research on PSSM has largely involved horses with type 1 PSSM. Current knowledge of type 2
PSSM is based on retrospective evaluation of cases diagnosed with PSSM by muscle biopsy that
are now known be free of the GYS1 mutation and a few years of prospective clinical cases.
Approximately 28% of cases of PSSM diagnosed by muscle biopsy in Quarter Horses do not
have the GYS1 mutation. Type 2 PSSM seems to be more common in higher performance horses
such as barrel racing, reining and cutting horses compared to the high prevalence of type 1
PSSM in halter horses. About 80% of cases of PSSM diagnosed by biopsy in Warmbloods have
type 2 PSSM. Breeds affected include Dutch Warmbloods, Swedish Warmbloods, Hanoverians,
Friesians, Selle Francais, Westfalian, Canadian Warmblood, Irish Sport Horse, Gerdlaner,
Hussien, and Icelandic horses. Many other light breeds have also been diagnosed with type 2
PSSM including Morgans, Standardbreds and Thoroughbreds. Type 2 PSSM also occurs in
Arabians, however, in my experience this breed is distinct in that it often has amylase-resistant
rather than amylase sensitive polysaccharide but is negative for the GYS1 mutation.

**Etiology:** The cause of type 2 PSSM is currently unknown. It may well be that there are a group
of conditions that have separate etiologies but share common findings of glycogen accumulation
and poor performance. A heritable predisposition is suspected in Quarter Horses but yet to be
proven.

**Acute Clinical signs:** Horses with type 2 PSSM do not necessarily have the same calm
temperament as horses with type 1 PSSM. In adults, acute clinical signs of rhabdomyolysis are
similar between type 1 and type 2 PSSM. Muscle atrophy after rhabdomyolysis is a common
complaint in Quarter Horses with type 2 PSSM. There are more Quarter Horses less than one
year of age reported with type 2 PSSM than type 1 PSSM and these foals may present with an
inability to rise or a stiff hind limb gait.
**Chronic clinical signs:** Chronic signs of type 2 PSSM are often most closely related to poor performance rather than recurrent ER and elevations in serum CK activity. An undiagnosed gait abnormality, sore muscles and drop in energy level and willingness to perform after 5-10 min of exercise are common complaints in Quarter Horses with type 2 PSSM. Warmbloods with type 2 PSSM have painful firm back and hindquarter muscles, reluctance to collect and engage the hindquarters, poor rounding over fences, gait abnormalities, and slow onset of atrophy. The mean age of onset of clinical signs in Warmbloods is between 8 and 11 years of age with the median CK and AST activity being 323 and 331U/L, respectively.

**Diagnosis:** Type 2 PSSM must be diagnosed by muscle biopsy where increased or abnormal PAS positive material that is usually amylase-sensitive is apparent particularly in subsarcolemmal locations. Determination of what constitutes an abnormal amount of amylase-sensitive glycogen can be subjective. False positive diagnosis is possible for type 2 PSSM in highly trained horses that normally have higher muscle glycogen concentrations or in formalin fixed sections which show a greater deposition of subsarcolemmal glycogen even in healthy horses. Other histopathological features that may be present with both type 1 and type 2 PSSM include muscle necrosis, macrophage infiltration of myofibers, regenerative fibers, and fiber atrophy. Some laboratories grade polysaccharide accumulation as mild, moderate, and severe where mild accumulation represents a category which has a higher chance of being a false positive diagnosis. Mild PSSM cases in particular should receive a full physical examination to ensure that there are not other underlying causes for performance problems.

**Management of Exertional Myopathies**

Regular daily exercise and daily turn out for as long as possible are key to the health of horses with chronic forms of ER. Diet change alone is not effective in managing chronic ER and must be combined with regular exercise.

The results of standardized nutrition trials for RER thoroughbreds and PSSM1 Quarter Horses show that provision of a diet with a reduced NSC content and higher fat content than conventional concentrates reduces serum CK activity. These dietary recommendations differ between RER and PSSM in that PSSM horses have lower caloric requirements and lower recommended starch and fat content as a % of daily DE. With RER this diet reduces indices of nervousness which appear to impact ER and with PSSM1 they enhance glycogen utilization and fat metabolism as an alternate energy source.

**Caloric balance:** A nutritionally balanced diet with appropriate caloric intake and adequate vitamins and minerals are the core elements of treating chronic forms of ER. For RER Thoroughbreds and Standardbreds in training, the challenge is usually supplying enough calories in a highly palatable form to meet their daily energy demands. This is in part because they often require >30 MCal of DE a day and because with their nervous temperament they may be more discriminating in their eating habits. Many horses with PSSM are easy keepers and may be overweight at the time of diagnosis. Adding excessive calories in the form of fat to an obese horse may produce metabolic syndrome and is contraindicated. If necessary, caloric intake should be reduced by using a grazing muzzle during turn-out, feeding hay with a low nonstructural carbohydrate content (NSC) at 1 to 1.5% of body weight, providing a low calorie ration balancer and gradually introducing daily exercise. Rather than provide dietary fat to an
overweight horse, fasting for 6 h prior to exercise can be used to elevate plasma free fatty acids prior to exercise and alleviate any restrictions in energy metabolism in muscle.

Selection of forage: Thoroughbred horses do not appear to show the same significant increase in serum insulin concentrations in response to consuming hay with an NSC of 17% as seen in Quarter horses. This fact combined with the high caloric requirements of racehorses may mean that it is not as important to select hay with very low NSC content in RER thoroughbreds as it is in PSSM horses. The degree to which the NSC content of hay should be restricted below 12% NSC depends upon the caloric requirements of a PSSM horse. Feeding a low NSC hay of 4% provides room to add an adequate amount of fat to the diet of easy keepers without exceeding the daily caloric requirement and inducing excessive weight gain.

Low starch high fat concentrates: A controlled trial using the first specialized feed developed for RER (Re-Leve 13% fat by weight and 9% NSC), determined that, NSC should be no greater than 20% of daily DE and 20-25% of daily DE should be provided by fat for optimal management of RER horses fed 30 MCal or more/day. The principle consideration for amount of fat fed to PSSM horses should be whether this provides excessive calories and additional weight gain. Fat can be added such that it constitutes 13% DE in the form of oil added to a ration balancer or hay cubes.

Protein supplements: Horses with type 2 PSSM, particularly those with decreased muscle mass may benefit from an amino acid supplement within 45 minutes of exercise. Supplements with Whey based proteins that have been shown to enhance muscle mass can be purchased from Progressive: Topline Xtreme http://www.prognutrition.com/pn/products/supplements/top-line-xtreme/index.jsp or Purina: Purina Supersport, among others.

Medication: Tranquilizers may be of value in treating excitable horses prone to RER. Dantrolene when given to RER horses 60 to 90 minutes prior to exercise appears to attenuate muscle damage. To date there are no tested management strategies for horses with MH, although dantrolene seems like a reasonable but expensive approach. Horses with both MH and PSSM have been shown to respond to high fat low starch diets although their response is not as favorable as horses with PSSM alone.

Conflict of Interest statement: Drs. Valberg, Mickelson and McCue own the license for PSSM testing and receive sales income from its use. Their financial and business interests have been reviewed and managed by the University in accordance with its conflict of interest policies. A portion of the profits from the sale of Re-Leve go to Dr. Valberg and her research.

References at: http://www.cvm.umn.edu/umec/lab/home.html