Polysaccharide Storage Myopathy

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Polysaccharide storage myopathy is a common cause of exertional rhabdomyolysis, muscle soreness, and weakness. The primary breeds affected are Quarter Horses, draft horses, and Warmblood breeds. In Quarter Horses, the disease is known to have a genetic basis. Providing a diet low in starch and high in fat and fiber in addition to gradually introducing daily exercise dramatically improves clinical signs. Author's address: Department of Veterinary Population Medicine, College of Veterinary Medicine, University of Minnesota, 1365 Gortner Avenue, St. Paul, MN 55108; email: valbe001@umn.edu.

1. Introduction

Glycogen-storage disorders are common causes of muscle pain, cramping, and myoglobinuria in humans.[1] Glycogen accumulates because of perturbation in muscle-energy metabolism that is caused by inherited enzyme defects in glycogenolysis, glycolysis, or energy regulation.[2,3] The first glycogen-storage disorder was recognized in horses in 1992 when the muscle biopsy technique was used to examine horses with exertional myopathies.[4] This glycogen-storage disorder was identified in Quarter Horse-related breeds (Quarter Horses, Paint Horses, and Appaloosas) and was termed polysaccharide storage myopathy (PSSM). It was characterized by two-fold higher glycogen concentrations in skeletal muscle as well as the presence of abnormal granular amylase-resistant inclusions in histological sections of muscle specimens.[4]

Since that time, many hundreds of horses have been diagnosed with PSSM. Several different acronyms have been used to describe this disorder including EPSM and EPSSM (both of which stand for equine polysaccharide storage myopathy).[5–8] The variety of acronyms used are in part related to preferences of different laboratories as well as to differences in the criteria used to diagnose PSSM.

2. Diagnosis

A definitive diagnosis of PSSM can only be made based on evaluation of a muscle biopsy.[4] Supportive evidence of PSSM in Quarter Horses includes clinical signs of exertional rhabdomyolysis, persistent elevations in serum creatine kinase (CK) and aspartate transaminase (AST) activities, and a minimum of a three-fold elevation in CK activity 4 h after an exercise test consisting of a maximum of 15 min lunging at a walk and trot.[9] Supportive evidence in draft and Warmblood breeds includes exercise intolerance, muscle atrophy, weakness, and some gait abnormalities without necessarily finding elevations in muscle enzymes.[7,10–12]

A muscle biopsy of any locomotor muscle that provides a 2 × 1-cm block of tissue for evaluation is often sufficient for analysis. The site most easily sampled in the field using an open surgical approach is the semimembranosus or semitendinosus muscle. Clinics that can rapidly process muscle for frozen sections often use a modified Bergstrom biopsy instrument inserted into the gluteal muscle through a

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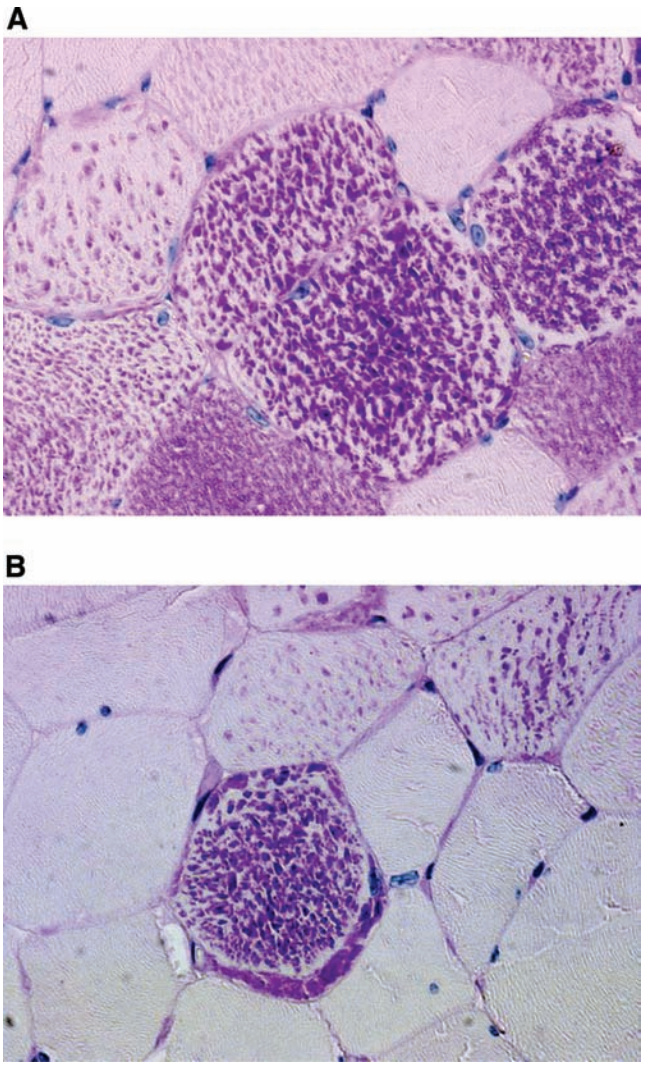

Fig. 1. (A) PAS stain of a semimembranosus muscle biopsy showing granular cytoplasmic inclusions of PAS-positive material. (B) Amylase PAS stain of the same muscle showing that much of PAS-positive material is resistant to amylase digestion.

1-cm incision. A diagnosis can be made irrespective of diet and proximity of sampling to recent episodes of rhabdomyolysis.

The characteristic features in histological sections include the presence of subsarcolemmal vacuoles, increased staining for amylase-sensitive glycogen in periodic acid Schiff's (PAS) stains, and the presence of amylase-resistant PAS positive abnormal polysaccharide inclusions in skeletal muscle fibers (Fig. 1, A and B).[4,7] These histologic features are readily identified in frozen muscle-biopsy sections, and biochemical assays have confirmed that muscle with abnormal polysaccharide accumulation has 1.8-fold higher muscle glycogen concentrations.[4,13] Laboratories using these criteria have used the acronym PSSM to describe the disorder.[4,5,9,14] Other laboratories processing muscle in formalin-fixed and, occasionally, frozen sections have used alternate diagnostic criteria and the acronym EPSM or EPSSM. The diagnostic criteria used by some laboratories have also included increased staining for amylase-sensitive glycogen in PAS stains or the presence of PAS-positive sarcoplasmic masses as the sole criteria for diagnosis of PSSM.[6,11,15–17] A much wider spectrum of breeds are diagnosed with PSSM using these alternate criteria.[6]

Inclusion of amylase-sensitive glycogen as a diagnostic criteria for PSSM greatly increases the sensitivity of the diagnostic test and reduces its specificity.[7,18] Because increased glycogen storage occurs as a normal response to training, it is commonly found near capillaries in normal horses.[18] Furthermore, because sarcoplasmic masses can be found in 60% of healthy horses,[19] normal horses may test positive with this method. In contrast, inclusion of amylase-resistant polysaccharide as a diagnostic criteria increases the specificity of a diagnosis for PSSM but can decrease the sensitivity of the test in young horses.[20] This should be taken into consideration when evaluating horses <2 yr of age, because clinical signs of rhabdomyolysis may precede the accumulation of abnormal polysaccharide in this age group.[20] Finally, if sufficiently large muscle samples are not evaluated, a false-negative diagnosis may occur because of the limited number of fibers with abnormal polysaccharide that occur in horses with PSSM. Thus, if a diagnosis of PSSM is made solely on increased staining for amylase-sensitive glycogen, the veterinarian should be aware of the high chance for a false-positive diagnosis; the horse should receive a full evaluation to ensure that there are not other underlying causes for performance problems.

3. Breed Prevalence

Many light breeds of horses, various draft breeds, ponies, Warmblood breeds, and mules are reported to have PSSM when amylase-sensitive glycogen is used as a diagnostic criterion for PSSM.[6,15–17] These criteria result in $>80\%$ of draft horses and 33% of all horses outside of draft and Quarter Horse bloodlines being diagnosed with PSSM.[6]

In contrast, Quarter Horse-related breeds, draft horses, and Warmbloods are the breeds most affected with PSSM when amylase-resistant abnormal polysaccharide is a required diagnostic criterion.[21] Of 1251 horses with a suspected neuromuscular disease, 40% were diagnosed with PSSM in a recent review of muscle biopsies.[21] Although >50 equine breeds were included in the study, 63% of horses with PSSM were of Quarter Horse-related breeds, 12% were draft breeds, and 9% were Warmblood breeds.[21]

4. PSSM in Quarter Horse–Related Breeds

Prevalence

A survey of 164 Quarter Horses used mainly for breeding or ranch work found that 6% of these

horses had PSSM based on identifying amylase-resistant abnormal polysaccharide in skeletal muscle biopsies.[22] These horses were kept on pasture, fed very little grain, and showed no clinical signs of a myopathy. In contrast, 23% of muscle biopsies of Quarter Horse-related breeds submitted to the Neuromuscular Diagnostic Laboratory (NDL) at the University of Minnesota because of signs of a neuromuscular disorder were diagnosed with PSSM.[21] PSSM seems to be a common cause of neuromuscular disease in Quarter Horse-related breeds; however, under certain environmental conditions, clinical signs may not be apparent.

Genetics

Although the prevalence of PSSM is 6% of Quarter Horses in general, it can be as high as 42% on some breeding farms.[22] This suggests that PSSM may be inherited within particular bloodlines. A familial basis for PSSM has been suggested from pedigree analysis and by limited breeding trials at the University of Minnesota.[5,20] Although pedigree analysis initially supported an autosomal recessive pattern of inheritance, identification of PSSM in Quarter Horse-crosses indicates that a dominant mode of inheritance is more likely.[6,21,22]

Clinical Signs

The average age of onset of clinical signs of PSSM is 5 yr in Quarter Horses, and it ranges from 1 to 14 yr of age.[8] There is no significant temperament, body type, or gender predilection for PSSM;[8] ~40% of owners feel that there is a seasonal pattern to the development of clinical signs. The most common trigger for clinical signs of PSSM is <20 min of exercise at a walk and trot, particularly if the horse has been rested for several days before exercise.[8] Signs of exertional rhabdomyolysis include firm painful muscles, stiffness, fasciculations, sweating, weakness, and reluctance to move. The hindquarters are frequently most affected, but back muscles, abdomen, and forelimb muscles may also be involved. During exercise, horses may stop and posture as if to urinate perhaps as a means to alleviate muscle cramping. Signs of pain can be particularly severe with 30% of horses exhibiting muscle pain for >2 h and ~5% of cases becoming recumbent.[8] Less common signs of PSSM in Quarter Horses include gait abnormalities, mild colic, and muscle wasting.

Quarter Horses frequently exhibit elevations of serum CK activity in association with clinical signs and possibly elevations of AST if rhabdomyolysis is chronic in nature.[4,8,23] The median CK and AST activity for all PSSM Quarter Horses with muscle biopsies submitted to the NDL at the University of Minnesota was 2809 and 1792 U/l, respectively. Persistent elevation in CK activity, despite an extended period of rest, is a common observation in PSSM-affected Quarter Horses.[24]

Pathogenesis

Common causes of glycogen-storage disorders, such as myophosphorylase deficiency, phosphofructokinase-enzyme deficiency, glycogen-branching enzyme deficiency, and adenosine monophosphate-kinase deficiency, in other species have been excluded as causes for PSSM in Quarter Horses.[13,14,25] The precise defect causing PSSM in Quarter Horses, however, remains to be identified. There seem to be at least two linked biochemical abnormalities associated with PSSM. The first abnormality is expressed as enhanced sensitivity to insulin in PSSM horses as determined by IV or oral glucose-tolerance tests as well as euglycemic hyperinsulinemic clamping.[26–29] In association with high dietary-starch intake, this enhanced insulin sensitivity may increase uptake of glucose into skeletal muscle and the subsequent formation of glycogen. Abnormal polysaccharide formed in PSSM skeletal muscle is less highly branched than normal glycogen and may reflect an imbalance in the heightened activity of glycogen synthase relative to the less tightly regulated glycogen-branching enzyme.[30] Abnormal polysaccharide is also occasionally found in the heart of PSSM horses but has not been identified in the liver.[26]

The development of rhabdomyolysis in PSSM horses is not directly associated with heightened insulin sensitivity.[29] If PSSM horses are treated with dexamethasone, their insulin sensitivity can be reduced to well within the normal range; however, they still develop rhabdomyolysis. Rather, muscle necrosis with exercise seems to be associated with a separate but potentially linked biochemical abnormality in energy metabolism. During submaximal exercise, muscle fibers in PSSM horses do not seem to generate adequate energy for muscle contraction, which is evidenced by the degradation of adenine nucleotides in individual muscle fibers.[31] Rhabdomyolysis is not characterized by marked accumulation of lactic acid.[13,31] Thus, it is likely that PSSM in Quarter Horses is caused by a defect in a regulatory pathway that controls both the flux of substrates, such as glucose into the cell, as well as the flux of substrates, such as glycogen and free fatty acids, through metabolic pathways during aerobic exercise.

5. PSSM in Draft Breeds

Prevalence

The prevalence of PSSM among draft breeds with biopsies submitted to the NDL at the University of Minnesota is 54%. The prevalence of PSSM is estimated at 80% based on review of necropsy samples from draft horses and the inclusion of the presence of increased amylase-sensitive glycogen as a diagnostic criterion.[6] The breeds most commonly diagnosed with PSSM at the NDL in Minnesota are Belgians, Percherons, and crosses of these breeds to light horses.[21] These are also the two most com-

mon draft breeds in the United States. To determine the true prevalence of PSSM in the Belgian horse population, a prospective study was performed by Firshman et al.[7] Muscle biopsies obtained from 113 Belgian horses on four farms revealed a prevalence of PSSM of 36% using amylase-resistant glycogen as the diagnostic criteria.

Genetics

The prevalence of PSSM did not vary between different Belgian breeding farms in the study by Firshman et al.[7] The notable sharing of bloodlines among all the horses in that study made pedigree analysis problematic in determining a pattern of inheritance. Several full- and half-sibling Belgian horses were identified with PSSM and many Belgian/light breed crosses have been identified with PSSM, indicating that further genetic studies of this disorder is warranted.

Clinical Signs

The average age of draft horses diagnosed with PSSM is 8 yr of age.[8,21] No particular gender predilection has been identified for PSSM in draft horses. It is notable that clinical signs are not consistently present with PSSM, because many of the Belgian draft horses that were positive for PSSM in the study by Firshman et al.[7] had no clinical signs. PSSM in draft horses likely is the same disorder described as "Monday Morning Disease" in work horses in the early 20th century.[32] Exertional rhabdomyolysis is a manifestation of PSSM in draft horses as well as draft crosses and can be so severe that it leads to recumbency and death.[11,32,33] In addition, post-anesthetic myopathy may also be a complication of PSSM in draft breeds.[10] A number of draft horses with PSSM present with signs of progressive weakness and muscle loss resulting in difficulty rising.[11,16] In these cases, serum CK activity is frequently normal. Gait abnormalities such as excessive limb flexion, fasciculations, and trembling are commonly seen with PSSM in draft horses.[11,16,21] Although the condition shivers was previously attributed to PSSM,[34] a recent study found no causal association between these two conditions.[7] The very high prevalence of PSSM in draft horses in essence means that there is a 36% chance that any clinical sign could be falsely associated with the disease PSSM. Thus, clinical judgment is required to determine whether the muscle biopsy results could reasonably be associated with a myopathic process or if other possible causes of muscle weakness or gait changes should also be investigated.

Serum muscle-enzyme activities are often normal in draft horses with PSSM.[7] The median serum CK and AST activity in draft horses from which biopsies were sent to the NDL at the University of Minnesota was 459 and 537 U/l, respectively. Mean CK and AST activities in the Belgian horse study by Firshman et al.[7] were 326 ± 380 and 355.0 ± 193 U/l, respectively. Serum vitamin E and whole-blood selenium concentrations are normal in draft horses with PSSM.[7]

Pathogenesis

Similar to Quarter Horses, muscle-glycogen concentrations in draft horses with PSSM are ~1.8-fold higher than in healthy horses.[7] In addition, abnormalities in enzymes involved in glycogenolysis or glycolysis have not been identified in draft breeds (unpublished observation). Unlike Quarter Horses with PSSM, Belgian horses do not seem to have heightened insulin sensitivity as evidenced by normal results during euglycemic hyperinsulinemic clamping.[35] Detailed studies of energy metabolism have not been performed in draft horses with PSSM and are necessary to further elucidate the biochemical basis for this disorder. Based on difference in clinical signs and physiological responses between draft and Quarter Horses, it cannot be assumed at this point that this glycogen-storage disorder is identical to that found in Quarter Horses.

6. PSSM in Warmbloods

Prevalence

The true prevalence of PSSM in other horse breeds remains to be established. Based on the number of horses diagnosed with PSSM from muscle biopsies submitted to the NDL in Minnesota, PSSM seems to be a common neuromuscular disorder in Warmblood horses with ~50% of Warmblood biopsies being diagnosed with PSSM.[21] This included a wide variety of Warmblood breeds such as Dutch Warmbloods, Hanoverian, Westfalian, Canadian Warmblood, Irish Sport Horse, Gerdlander, Hussien, and Rheinlander.

Genetics

No reports on the potential inheritance of PSSM in Warmbloods have been published.

Clinical Signs

The mean age of onset of clinical signs in Warmbloods is reported to be between 8 and 11 yr of age.[12,21] A gender predilection for PSSM has not been identified.[21] The most common clinical signs reported in Warmbloods with PSSM are painful firm back and hindquarter muscles, reluctance to collect and engage the hindquarters, poor rounding over fences, gait abnormalities, and atrophy.[12,21,36] Overt signs of exertional rhabdomyolysis, such as stiffness, shortness of stride, and reluctance to move after exercise, were reported in <15% of Warmbloods with PSSM.[21]

The median CK and AST activity for Warmbloods diagnosed with PSSM at the NDL in Minnesota is 323 and 331 U/l, respectively.

Pathogenesis

Little is known about this form of PSSM, because no biochemical or physiological studies have been per-

formed in Warmbloods with polysaccharide-storage myopathy.

7. PSSM in Other Breeds

A small number of horses of other breeds have been reported to have PSSM. The prevalence of PSSM within these breeds seems to be quite low. For example, although >50% of biopsies of Quarter Horses, draft horses, and Warmbloods were diagnosed with PSSM, <10% of muscle biopsies from 178 Thoroughbreds, 40 Arabians, and 32 Standardbreds with neuromuscular disease were diagnosed with PSSM. A slightly higher prevalence was found for Morgan and Tennessee Walking Horses.[21] Previous published reports of PSSM based on amylase-resistant polysaccharide include small numbers of horses of Warmblood cross, Anglo-Arab, Andalusion, Morgan, Arabian, Welsh cross, and Standardbred breeds.[6] Some of the controversy regarding the number of breeds affected with PSSM may be a result of inclusion of cases with sarcoplasmic masses and increased PAS staining for glycogen as horses positive for PSSM.[6]

8. Management of PSSM

Owners need to be aware that any horse diagnosed with PSSM will always have an underlying predilection for muscle soreness. The best that can be done is to manage horses in the most appropriate fashion to minimize clinical signs. With adherence to both the diet and exercise recommendations provided below, at least 80% of horses show notable improvement in clinical signs; many return to acceptable levels of performance.[8,12,16] There is, however, a wide range in the severity of clinical signs shown by horses with PSSM. Those horses with severe or recurrent clinical signs will require more stringent adherence to diet and exercise recommendations to regain muscle function.

Rest

PSSM horses that are confined for days to weeks after an episode of rhabdomyolysis often have persistently elevated serum CK activity.[24] In contrast, PSSM horses kept on pasture with little grain supplementation often show few clinical signs of rhabdomyolysis and have normal serum CK activity.[20,22] As a result, a common recommendation for horses with PSSM is to limit stall confinement to <48 h after an episode of rhabdomyolysis and then provide turnout in paddocks of gradually increasing size. Providing horses with as much free exercise as possible on pasture seems to be beneficial in the long term. After an acute episode, excitable horses may require tranquilization before turnout to avoid excessive galloping. Hand-walking horses recovering from an episode of PSSM for >5–10 min at time may trigger another episode of rhabdomyolysis.

Exercise Regimens

Important principles to follow when starting exercise programs in PSSM horses include (1) provide adequate time for adaptation to a new diet before commencing exercise, (2) recognize that the duration of exercise, not the intensity, is of primary importance, (3) ensure that the program is gradually introduced and consistently performed, and (4) minimize any days without some form of exercise.[8,24] If horses have experienced an episode of rhabdomyolysis recently, 2 wk of turnout and diet change are often beneficial before recommencing exercise. Exercise should be very relaxed, and the horse should achieve a long, low frame without collection. For many horses, this is most readily done in a round pen or on a lunge line. Successive daily addition of 2-min intervals of walk and trot, beginning with only 4 min of exercise and working up to 30 min, after 3 wk is often recommended.[8,12,24] Owners often do not recognize that walking the horse for 10 min or more initially can trigger muscle soreness in PSSM horses. Advancing the horse too quickly often results in an episode of rhabdomyolysis and repeated frustration for the owner. Work can usually begin under saddle after 3 wk of ground work and can gradually be increased by adding 2-min intervals of collection or canter to the initial relaxed warm-up period at a walk and trot. Unless a horse shows an episode of overt rhabdomyolysis during the initial first 4 wk of exercise, reevaluating serum CK activity is not usually helpful for the first month. This is because it is very common to have subclinical elevations in CK activity when exercise is reintroduced, and a return to normal levels often requires 4–6 wk of gradual exercise.[23,24] Keeping horses with PSSM fit seems the best prevention against further episodes of rhabdomyolysis.

This gradual approach to reintroducing exercise aims to enhance the oxidative capacity of skeletal muscle without causing further cellular damage. The oxidative capacity of locomotor muscles in most Quarter Horses is very low but can be increased with daily exercise.[23,26] The objective of enhancing oxidative metabolism is to facilitate the metabolism of fat as an energy substrate.

Dietary Management of PSSM

The dietary modification for PSSM horses is designed to reduce the glucose load and provide fat as an alternate energy source. Anecdotally, owners report that this type of diet improves clinical signs of muscle pain, stiffness, and exercise tolerance in draft horses, Warmbloods, Quarter Horses, and other breeds.[8,12,16] Dietary change seems to have less impact on alleviating gait changes such as shivers.[12] The value of low-starch, high-fat diets in reducing exercise-induced muscle damage has only been shown under controlled experimental conditions in Quarter Horses.[23] In PSSM Quarter Horses with increased sensitivity to insulin, dropping dietary starch to <10% of daily digestible energy and increasing dietary fat to 13% of daily digestible energy resulted in normal serum CK activity 4 h post-exercise during a 6-wk trial. Provi-

Table 1. Feeding Recommendations for an Average-Sized Horse (500 kg) with PSSM at Various Levels of Exertion

	Maintenance	Light Exercise	Moderate Exercise	Intense Exercise
Digestible energy (Mcal/day)	16.4	20.5	24.6	32.8
% DE as NSC	<10%	<10%	<10%	<10%
% DE as fat	20%	20%	15%–20%	15%–20%
Forage % bwt	1.5–2.0%	1.5–2.0%	1.5–2.0%	1.5–2.0%
Protein (grams/day)	697	767	836	906
Calcium (g)	30	33	36	39
Phosphorus (g)	20	22	24	26
Sodium (g)	22.5	33.5	33.8	41.3
Chloride (g)	33.8	50.3	50.6	62
Potassium (g)	52.5	78.3	78.8	96.4
Selenium (mg)	1.88	2.2	2.81	3.13
Vitamin E (IU)	375	700	900	1000

Daily requirements derived from multiple research studies (% NSC = starch and sugar in the concentrate) and Kentucky Equine Research recommendations.

sion of similar fat content and higher starch content resulted in increased serum CK activity in the most severely clinically affected horses. The beneficial effect of the low-starch, high-fat diet in this study[a] was believed to be the result of less glucose uptake into muscle cells and provision of more plasma-free fatty acids in muscle fibers for use during aerobic exercise.[23] Quarter Horses naturally have very little lipid stored within muscle fibers and provision of free fatty acids may overcome the disruption in energy metabolism that seems to occur in PSSM Quarter Horses during aerobic exercise.[31] Studies clearly show, however, that these dietary changes alone are not beneficial, and an exercise program must be instituted for PSSM horses to show clinical improvement.[8,12] Further controlled experimental studies of the physiological effect of low-starch, high-fat diets are necessary in other breeds of horses with PSSM to determine how and if they truly have a beneficial effect.

Forage and pasture provide the foundation for the diet of PSSM horses. To date, the significance of the starch and sugar content of hay or pasture on clinical signs of PSSM is not known. Anecdotally, some horses seem to have an increased incidence of rhabdomyolysis when on lush pasture. Thus, it seems reasonable to limit exposure to lush pastures. Hay that has a moderate to low content of soluble sugars and non-fermentable starch and fewer gluconeogenic amino acids would seem the best choice for PSSM horses. Second cutting of grass hay, Brome hay, or oat hay may be the best choice for most PSSM horses.

The caloric needs of the horse should be assessed first to determine the amount of hay as well as low-starch, high-fat concentrates that the horse should be fed. Provision of excessive calories in the form of fat to overweight horses is detrimental. For overweight horses, restricting hay to 1% of body weight and limiting access to pasture grass while increasing daily exercise may be beneficial. In addition, selection of a low-starch, fat-supplemented feed that is particularly high in dietary fiber may be the best means of providing dietary fat without causing excessive weight gain. PSSM horses that have normal body weight can be fed forage at the rate of 1.5–2% of body weight.

A wide variety of low-starch, high-fat diets are available for horses. The most important dietary principle seems to be that of the total daily calories required or digestible energy (DE); <10% should be supplied by starch, and ≥13% should be supplied by fat. Some authors recommend that 20% of daily caloric intake be supplied by fat (0.5 kg of fat) based on clinical experiences,[16] whereas others report improvement in clinical signs when 10–15% of DE is supplied as fat.[8,12,23,37] There is a great deal of variation in individual tolerance to dietary starch; however, horses with more severe clinical signs of PSSM seem to require the greatest restriction in starch intake.[23]

A number of well-balanced, low-starch, high-fat commercial diets are suitable for horses with PSSM. There is, at present, no research to suggest that one form of fat is more beneficial than another. Some commercial feeds meet the recommended nutritional needs of PSSM horses in one pelleted ration. These feeds typically contain >10% of fat by weight and <20% of starch or non-structural carbohydrate (NSC) by weight. Some feed companies offer similar nutritional content by blending their manufactured feeds or by supplementing with oils or rice bran. Palatability of pelleted feeds is usually higher than feeds containing oils or loose rice bran. At present, the NSC content of equine-feed products is not listed on the feed tag, and consultation with the feed manufacturer is necessary to obtain this information. Nutritional support is available through most feed manufacturers in designing an appropriate diet using the recommendations provided in Table 1. The NDL provides a list of sug-

gested diets together with the results of muscle-biopsy evaluation.

Expectations of Fat Supplementation

The time required for improvement in signs of exertional rhabdomyolysis is controversial. Serum CK activity declined to normal in PSSM Quarter Horses within 3 wk of beginning a high-fat, low-starch diet combined with regular daily exercise.[23] Others have suggested that a minimum of 4 mo of supplementation is required.[16] Firshman et al.[8] found that 75% of Quarter Horses showed clinical signs of improvement when both diet and exercise were changed; however, significantly fewer horses showed improvement if dietary changes were instituted without introducing a gradually increasing exercise regime. Hunt et al.[12] found the 54% of Warmbloods showed improved clinical signs if both diet and exercise regimens were followed.

A portion of the profits from the sale of Re-Leve are donated to the University of Minnesota.

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