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Current status of myopathies affecting athletic horses

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REVIEW ARTICLE

Abstract

Muscular disorders rank among the most prevalent problems of horses competing in a broad variety of athletic disciplines, including track racing, dressage, endurance racing and Western riding disciplines. As described in this review, active scientific investigation is continuing to elucidate the different mechanisms underlying specific muscular disorders in horses, and is discovering and defining new disorders, and new methods of diagnosis, treatment and management. The flourishing field of equine rehabilitation and regenerative medicine is also driving the progressive application of a variety of modalities to the treatment and management of musculoskeletal conditions in horses. However, it is essential that this be accompanied by appropriate scientific investigation to verify the efficacy of recommended modalities and treatment protocols.

Keywords: equine, rhabdomyolysis, polysaccharide, dantrolene

1. Introduction

Muscular disease continues to be a common cause of morbidity and occasional mortality in horses participating in a variety of athletic disciplines. Dedicated investigation over several decades has greatly advanced the characterisation and understanding of specific disorders. However, important questions remain unanswered, new diagnostic methods are constantly under development, and novel information is continuously emerging (Valberg, 2012). A number of detailed reviews of equine muscular disorders are available in the scientific literature (Aleman, 2008; Mickelson and Valberg, 2015; Valberg, 2012); the current article will therefore focus on recent developments in the understanding, diagnosis and management of specific muscle disorders relevant to athletic horses.

Muscle tissue comprises a proportionally greater amount of body mass in horses compared to other athletic species, often representing over 50% of bodyweight and dominating the demand for energy and cardiac output during exercise (Piercy and Rivero, 2014). Equine muscle is also comprised of a high proportion of fast twitch muscle fibres (type IIA and IIX and their hybrids), permitting the generation of phenomenal speed and power, but potentially also increasing susceptibility to injury (Piercy and Rivero, 2014). Furthermore, equine athletes are subject to technically and physically demanding activities under the direction of a rider or driver, which can promote vulnerability to muscular injury during traumatic incidents or activities that exceed the horse's level of preparation.

Complicating the picture is also the fact that selective breeding in specific athletic disciplines has propagated several hereditary muscular disorders, perhaps particularly so in Thoroughbreds, Standardbreds and Quarter Horses (Mickelson and Valberg, 2015). Underscoring this contribution of genetic selection processes to muscular disease, a recent study identified high allele frequencies for polysaccharide storage myopathy (PSSM), hyperkalemic periodic paralysis (HYPP), and glycogen branching enzyme deficiency (GBED) in a population of elite American Quarter Horses (Tryon *et al.*, 2009). As more convenient and reliable methods of testing for specific hereditary disorders become available, veterinarians must develop their role in guiding responsible genetic selection of breeding stock. Nonetheless, it must also be accepted that some muscular disorders are inadvertently or deliberately selected for because of favourable accompanying characteristics (Mickelson and Valberg, 2015). Therefore a substantial

proportion of certain athletic horse populations are currently afflicted with muscular disorders, and this phenomenon is likely to persist in future (Mickelson and Valberg, 2015). Examples of positive selection pressure for muscular disorders in horses include selection for superior muscling in Quarter Horses with HYPP, selection for lower maintenance energy requirements in horses with PSSM, and the association of exertional rhabdomyolysis with superior performance variables in Standardbred racehorses (Isgren *et al.*, 2010; McCoy *et al.*, 2014; Mickelson and Valberg, 2015; Naylor, 1994). Continued investigations into improving diagnostic methods and management strategies for equine muscle disorders will therefore remain of great relevance in athletic horse populations.

2. Specific muscular disorders of athletic horses

Muscle strain and trauma

Similarly to human athletes, equine athletes are at substantial risk of impact injuries or over-exertion, which can readily create local muscle strain or trauma, or sometimes more generalised damage (Piercy and Rivero, 2014; Walmsley *et al.*, 2010). Anaesthetic myopathy and compartment syndrome represent other traumatic muscular conditions that can create severe damage (Nelson *et al.*, 2015, Wagner, 2008). Predisposing factors for muscle strain in horses might include the activity performed, early season competition, pre-existing lameness or injury, lack of warm-up exercise, and covering challenging or downhill terrain which demands eccentric contractions from the musculature.

Definitively identifying and/or confirming muscle strain or tears can be particularly challenging since clinical signs are often subtle, and can include non-specific lameness, reluctance to perform certain activities, or pain in response to muscular palpation (Piercy and Rivero, 2014). More significant strain may promote overt lameness and heat and swelling of the affected musculature, sometimes with a palpable defect (Walmsley *et al.*, 2010). Repeated injury over time to a specific muscle group can result in fibrosis and ossification, resulting eventually in mechanical lameness. Definitive diagnosis of muscle injury is infrequently achieved, a situation which might reflect poorly specific clinical signs and the limited ability of imaging modalities such as ultrasonography and thermography to reliably detect mild to moderate muscular injury. More sensitive imaging modalities such as magnetic resonance imaging and particularly nuclear scintigraphy have utility for diagnosis of muscular damage in horses, but present significant practical challenges which currently obviates their routine use (Morris *et al.*, 1991; Swor *et al.*, 2001; Walmsley *et al.*, 2010). Although serum biochemical analysis can be supportive of muscular injury, findings are influenced by timing of assessments and the muscle mass affected. Therefore a diagnosis of muscle strain is often tentative, and is typically made from history, clinical suspicion and the exclusion of other disorders.

Horses with suspected or confirmed muscle strain require modification of exercise activity for days to months, depending on the type and severity of injury incurred. Prolonged immobility should be avoided since it might promote scarring and contracture (Toppin and Lori, 2006; Walmsley *et al.*, 2010). Anti-inflammatory drugs are often provided in the acute stages to reduce discomfort and to encourage normal motion, which in itself helps reduce pain and stiffness. However, there is growing evidence that non-steroidal anti-inflammatory drugs inhibit muscle healing through their influence on muscle satellite cells and macrophages, a phenomenon which has been minimally investigated in horses but which should be considered (Mackey *et al.*, 2012). Icing affected muscles might provide analgesic and anti-inflammatory effects, and can be performed for 10 minutes at a time for superficial injuries and for up to 20 minutes at a time for deeper injuries when the affected region is of feasible size for this form of treatment. Accessory modalities that have been used for the purpose of providing analgesia and/or facilitating healing and return of function include therapeutic ultrasound, cold laser, acupuncture, massage and therapeutic stretching (Kaneps, 2016; Walmsley *et al.*, 2010). Combinations of these therapies might be particularly useful for severe focal injuries, however there is a paucity of scientific information supporting the efficacy of therapies such as cold laser and therapeutic ultrasound for equine muscle injury. The penetration depth for both of these modalities is likely a significant limiting factor to their utility in the horse (Duesterdieck-Zellmer *et al.*, 2016; Montgomery *et al.*, 2013). Severe muscular injuries might also benefit from the use of muscle relaxants, including methocarbamol or dantrolene sodium. The pharmacokinetics of both agents have been demonstrated in horses, though clinical efficacy for muscle injury is better supported for dantrolene, which also prevents muscle necrosis (Court *et al.*, 1987; Edwards *et al.*, 2003; Flacco *et al.*, 1989; McKenzie *et al.*, 2004; Rumpler *et al.*, 2014). Additional pharmaceutical agents are under evaluation in human athletes for prevention of muscle fibrosis in healing muscle injuries, however they have not been studied intensively, and as yet, have not been evaluated for this purpose in horses (Garg *et al.*, 2015).

As recovery from injury progresses, horses should be cautiously returned to exercise. A thorough, targeted warm-up routine should be developed to appropriately prepare the musculature for specific activities to decrease the risk of injury (Walmsley *et al.*, 2010). Appropriate development of cumulative training volume likely reduces risk of muscular injury in horses, as evidenced by the greater incidence of muscle strain in polo ponies early in the competition season, and in racehorses performing unaccustomed exercise (Mack

et al., 2014; McGowan *et al.*, 2002b). Training frequency should also be considered, since higher post exercise serum muscle enzyme activity has been reported in horses training two compared to three times per week (Lindner *et al.*, 2006). However, even with adequate preparation, some degree of muscle strain is likely to occur in healthy conditioned horses participating in challenging or prolonged athletic events. A recent study demonstrated that mild to moderate elevations in serum creatine kinase (CK) of up to several thousand U/l are commonly observed in racing endurance horses, comparable to changes induced by long distance running in human and canine athletes (Fallon *et al.*, 1999; McKenzie *et al.*, 2007; Wilberger *et al.*, 2015).

Athletic horses are potentially also more prone to local or generalised muscle damage during general anaesthesia; particularly horses with pre-existing exertional rhabdomyolysis disorders, or those heterozygous for the mutation in the ryanodine receptor (*RyR1*) associated with equine malignant hyperthermia (MH) (Aleman *et al.*, 2004; Mickelson and Valberg, 2015). In a survey by the author of over 100 horses anaesthetised at four teaching hospitals, 6% of horses undergoing general anaesthesia developed serum CK values greater than 6,000 U/l after anaesthesia, and horses with a prior history of exertional rhabdomyolysis had significantly higher serum CK after anaesthesia than horses without such a history (unpublished data). Clinical signs of anaesthetic myopathy are typically evident during or soon after anaesthetic recovery, which may in itself be violent or difficult. Other signs include difficulty standing and moving, reduced weight bearing on affected limbs, fasciculations, distress, and pain, swelling and firmness of the affected muscles (Wagner, 2008). Signs of MH in horses include hyperthermia, tachycardia, sweating, myoglobinuria and rigidity (Aleman *et al.*, 2004).

Clinical observations suggest that serum CK activity in horses with anaesthetic myopathy is often only mildly elevated at the onset of clinical signs, but frequently increases over 24 to 48 h, and can exceed 100,000 U/l in severe cases. Affected horses should therefore be treated promptly and aggressively if disease is suspected, to limit muscle swelling (which can damage peripheral nerves and compound pain and muscle necrosis), and to control pain and to reduce the deleterious effects of myoglobinuria. Depending on the severity of disease the provision of intravenous or oral fluids, anti-inflammatory and analgesic drugs, and treatment with dantrolene sodium (4 to 6 mg/kg, q 8 to 12 h, PO to a recently fed horse) should be considered. Horses should be encouraged to stay standing and may require sling support. Serial monitoring of myoglobinuria and muscle enzyme activity should be performed. Recovered animals frequently develop atrophy of the affected area which may resolve over time.

Prevention of anaesthetic myopathy includes provision of adequate padding during general anaesthesia, appropriate duration of anaesthesia, careful limb positioning to protect dependent musculature, and maintaining mean arterial pressure (Wagner, 2008). Premedication with dantrolene sodium has been evaluated in clinical trials, and appears to reduce post anaesthetic serum CK activity when compared to placebo in crossover trials (McKenzie *et al.*, 2015). However, a recent study reported reduced cardiac output, hyperkalemia and accompanying cardiac arrhythmias in dantrolene pre-medicated horses (McKenzie *et al.*, 2015). Therefore pre-medication with dantrolene should be performed cautiously when indicated, followed with serial monitoring of plasma potassium concentrations, and should be avoided in any horse with possible HYPP. Furthermore, it should be noted that dantrolene is not well absorbed in horses deprived of feed prior to administration (McKenzie *et al.*, 2010).

Exertional myopathy disorders

The increasing body of information regarding exertional rhabdomyolysis (ER) disorders in horses has resulted in a tendency to evaluate this syndrome clinically and diagnostically based to some degree on the breed of the affected horse (Mickelson and Valberg, 2015). This is related to the likelihood of clinical signs of ER reflecting an underlying heritable muscular disorder in many breeds (Aleman, 2008; Mickelson and Valberg, 2015; Valberg, 2012). Evaluating ER in this manner often promotes a more rapid and less invasive diagnostic approach, particularly in breeds with a high prevalence of PSSM, which can be readily identified by testing for the causative genetic mutation (Aleman, 2008; Mickelson and Valberg, 2015; Valberg, 2012). However, in other athletic breeds, the underlying causes and most appropriate methods of diagnosing and managing ER have not been fully determined. Consequently, more invasive diagnostic measures such as surgical muscle biopsy are often indicated, and disease management often requires organised attempts to identify triggering factors for clinical disease that might be subsequently manipulated (Piercy and Rivero, 2014; Valberg, 2012). Further clarification of the cause of ER is necessary for Thoroughbred, Standardbred, Arabian and Warmblood horses at this time (Mickelson and Valberg, 2015; Valberg, 2012). Furthermore, the role that exertional myopathy disorders might play in the occurrence of other muscular diseases, including anaesthetic myopathy, remains unclear.

Polysaccharide storage myopathy

PSSM, first recognised in Quarter Horses in 1992, is arguably now the most well characterised exertional rhabdomyolysis disorder of horses (Mickelson and Valberg, 2015). Affecting a wide variety of light and draft breeds, disease primarily relates to heterozygosity for a gain of

function mutation in the glycogen synthase 1 (*GYS1*) gene, resulting variably in exertional rhabdomyolysis, muscle atrophy, weakness or other signs of dysfunction (Valberg, 2012). Clinical disease can be exacerbated by homozygosity for the *GYS1* mutation, or by the concurrent presence of the *SCNA4* mutation associated with HYPP or the *RyR1* mutation associated with MH (Mickelson and Valberg, 2015). Identification of the *GYS1* and *RYR1* mutations has greatly improved evaluation of horses with suspected PSSM by allowing testing of hair or blood samples versus histopathologic analysis of skeletal muscle biopsies. Affected horses typically have elevated muscle glycogen concentrations and abnormal accumulations of amylopectin within skeletal muscle and occasionally cardiac muscle fibres (Maile *et al.*, 2017; Mickelson and Valberg, 2015; Valberg, 2012).

The pathogenesis of muscle damage in horses with PSSM has not yet been fully elucidated. A recent study using *in silico* characterisation and enzyme homology modelling demonstrated a probable model for constitutive activation of the mutant glycogen synthase enzyme (Maile *et al.*, 2017). Muscle damage is thought to relate to an aerobic energy deficit during exercise, which appears to be supported to some degree by initial gene expression studies, however, additional work is necessary (Annandale *et al.*, 2005; Barrey *et al.*, 2009; Mickelson and Valberg, 2015).

Recurrent exertional rhabdomyolysis

This exertional rhabdomyolysis syndrome is believed to occur in both Thoroughbred and Standardbred horses and to have analogous aetiology in these breeds, although investigations continue in an attempt to clarify the underlying cause (Aleman, 2008; Isgren *et al.*, 2010; Piercy and Rivero, 2014). Affected horses tend to show stiffness, sweating and muscle pain associated with exercise. Both breeds are significantly more likely to develop clinical signs during or after training exercise, and rarely during racing (Isgren *et al.*, 2010; MacLeay *et al.*, 1999). A predilection for female gender and nervous temperament is also reported in both breeds, and episodes are commonly preceded by rest from exercise of variable duration (Isgren *et al.*, 2010; MacLeay *et al.*, 1999).

A variety of studies, including epidemiologic, *in vitro* and *in vivo* studies have strongly suggested a heritable abnormality of calcium kinetics within skeletal muscle cells as the cause of disease in Thoroughbred horses (Valberg, 2012). A recent study using SNP genotyping data was able to demonstrate a similar and moderate degree of heritability in Thoroughbreds and Standardbreds with suspected RER (Norton *et al.*, 2016). However, despite extensive investigations since 1999, causative mutations remain elusive, suggesting more complex associations than Mendelian inheritance for this disorder (Norton *et al.*, 2016; Mickelson and Valberg, 2015). As a result, diagnosis is currently still based on signalment, clinical signs, and inappropriate increases in serum CK with exercise. Skeletal muscle biopsy often reveals non-specific findings consistent with chronic myopathic change, making this procedure of questionable value in many cases (Valberg, 2012). Recently, a skin derived equine myotube model has been developed which shows great promise as a potential avenue for further investigation of the pathophysiology of this disorder and for the study of potential pharmaceutical treatments (Fernandez-Fuente *et al.*, 2014).

Myofibrillar myopathy

Recent investigation of Arabian horses in the United States identified a substantial prevalence of ER in horses racing 80 km distance events (Wilberger *et al.*, 2015). Clinical signs of rhabdomyolysis in this breed have been reported to occur during training and racing, and can be subtle, consisting of mild stiffness and red urine, or they can be overt, with cramping, sweating, reduced speed, and delayed heart rate recovery (McKenzie *et al.*, 2016; Wilberger *et al.*, 2015). Serum CK can be substantially elevated, exceeding 100,000 U/l, despite very mild clinical signs in some cases (Wilberger *et al.*, 2015). A period of rest preceding exercise appears to be a strong triggering factor, and can be as short as two days of rest after a racing event, with signs of muscle pain occurring within minutes in some horses when light training is resumed (McKenzie *et al.*, 2016). Affected Arabians lack the studied *GYS1* and *RYR1* mutations, although a heritable disorder is strongly suspected (Wilberger *et al.*, 2015). Exercise testing of affected Arabians supports normal metabolic regulation through evaluation of muscle glycogen and blood lactate concentrations, with gene expression profiles yet to be evaluated (McKenzie *et al.*, 2016). Formalin fixed and frozen skeletal muscle tissue sections from affected horses display myopathic changes, with a greater frequency of central nuclei, glycogen aggregation, and disrupted myofibrillar alignment. Additionally, a characteristic feature appears to be cytoplasmic aggregation of the protein desmin, recognised primarily via specialised histochemical staining techniques that are not routinely employed (McKenzie *et al.*, 2016; Valberg *et al.*, 2015). Affected horses also have normal muscle glycogen concentrations (McKenzie *et al.*, 2016). It was concluded that myofibrillar disruption in the skeletal muscle fibres of these horses results in atypical glycogen pooling, which previously has led to erroneous diagnosis of a glycogen storage disorder, referred to as type 2 PSSM, in some Arabian horses (Valberg *et al.*, 2015). It is now thought however, that type 2 PSSM represents instead, a myofibrillar myopathy type condition (MFM) (Valberg and McKenzie, 2016; Valberg *et al.*, 2015). Further investigations of this disorder are continuing with attempts underway to identify a causative genetic mutation through genome wide sequencing.

A variety of light breeds and also Warmblood breeds, including Hanoverians, Friesians, Westphalians, and Dutch and Swedish Warmbloods, have also previously been reported to have type 2 PSSM. This was based on the fact that affected horses typically lacked the *GYS1* mutation associated with PSSM, despite the presence of glycogen aggregates within muscle cells on histopathologic assessment (McCue *et al.*, 2009). Furthermore, biochemically assessed muscle glycogen concentrations in horses with purported type 2 PSSM are normal rather than increased. Affected Warmblood horses have been reported to display signs of exertional rhabdomyolysis, but much more frequently present with complaints that include nebulous gait anomalies, poor technical performance, and reduced enthusiasm for exercise. Serum muscle enzyme activity is often unremarkable (Valberg, 2012). Recent evidence suggests that type 2 PSSM is analogous with the newly characterised myofibrillar myopathy of Arabian horses (Valberg and McKenzie, 2016; Valberg *et al.*, 2015, in press). This is based on similarities in muscle biopsy findings despite differences in clinical signs, with muscle atrophy a much more consistent clinical feature of disease than rhabdomyolysis in Warmblood horses (Valberg and McKenzie, 2016). Similarly, a recent report indicates that muscle atrophy is a common clinical sign of disease in Andalusian horses diagnosed with idiopathic exertional rhabdomyolysis (Chamizo *et al.*, 2015). Muscle biopsies from these horses do not appear to have been assessed for desmin staining patterns, which might open the possibility of an analogous disorder to MFM in the Andalusian breed.

3. Advances in diagnostic methods

A rapidly expanding array of investigative techniques is being utilised in the study of various equine muscular disorders. They have been aimed largely at investigating the aetiology and pathophysiology of specific diseases, which ultimately would be expected to assist the development of more convenient diagnostic tests or more appropriate treatment or management strategies. The identification of specific genetic mutations and the ability to test for them has represented a significant advance, since it reduces the invasiveness of diagnostic assessment of these disorders. Reliable genetic testing is currently available for HYPP, GBED, MH and PSSM (Mickelson and Valberg, 2015; Valberg, 2012). Causative mutations remain elusive for RER despite intensive efforts, and have also not yet been defined for type 2 PSSM/MFM. There are currently no scientifically validated genetic tests described for these disorders, though companies exist that offer genetic testing for these diseases. Nonetheless, the successful sequencing of the equine genome has accelerated processes involved in identifying problematic mutations relevant to equine muscular disorders. Similarly, it will also likely accelerate identification of horses with superior athletic potential, which has already commenced with commercial testing for select polymorphisms associated with racing performance (Mickelson and Valberg, 2015; Rivero and Hill, 2016; Tozaki *et al.*, 2010).

The muscle biopsy procedure still maintains significant utility in evaluating equine muscular disorders of poorly characterised nature, and it has been a routine preliminary step in the identification of most major equine muscular disorders to date (Valberg, 2012). The addition of new staining techniques expands the ability to analyse muscular disorders and was a key feature of defining MFM in Arabian horses, and subsequently Warmblood horses in recent studies (McKenzie *et al.*, 2016; Valberg and McKenzie, 2016; Valberg *et al.*, 2015, in press). Large tissue samples collected by open surgical biopsy of the semimembranosus or semitendinosus muscles are still typically obtained in clinical evaluations where shipping to a laboratory is required. Percutaneous needle biopsies from the gluteal or other muscles is favoured in research situations, to provide tissue for histopathological and biochemical evaluations (Valberg, 2012). Microbiopsy techniques have been described which can provide small muscle samples for a variety of purposes, including culture of equine myoblasts, and high resolution respirometry and transcriptome analysis studies in horses with exertional rhabdomyolysis (Barrey *et al.*, 2012; Ceusters *et al.*, 2012; Houben *et al.*, 2015).

A variety of other technologies applicable to the study of muscle function and disease are being utilised in horses. Initial evaluation of multi-frequency bioimpedance has been reported as a method of assessing the effects of training and injury on equine muscle (Harrison *et al.*, 2015). Similarly, quantitative electromyography may be useful in the evaluation of specific equine myopathies (Wijnberg and Franssen, 2016). Muscular micro-RNA expression has been studied in horses with PSSM and RER, and ultrastructural mitochondrial alterations have been evaluated in horses with myopathy using transmission electron microscopy (Barrey *et al.*, 2010; Van Driessche *et al.*, 2015). Furthermore, gene expression studies are being progressively employed to evaluate and compare the responses to exercise of healthy horses and horses with muscle disease (Barrey *et al.*, 2006; Ghosh *et al.*, 2016). The rapidly expanding array of diagnostics will improve the understanding of the aetiology and pathophysiology of many equine muscular disorders and should facilitate the development of new treatment or management approaches.

4. Advances in treatment and management of myopathy disorders

Despite improved understanding of the aetiology and pathophysiology of several equine muscular disorders, advances in treatment and prevention have been surprisingly limited. Clinical trials have supported the

efficacy of alterations in rations and exercise regimes for the control of PSSM and RER, however, such management recommendations are not necessarily always practical, and performance impact is a concern with dietary alterations in track racing Thoroughbreds (Valberg, 2012). Furthermore, owner compliance is highly variable and clinical disease in severely affected horses can be challenging to control. Nonetheless, clinical signs of PSSM can be modified in a high proportion of affected horses with careful management including pasture turnout, a slow and progressive increase in daily exercise, and provision of ration that provides ≤10 % of the daily digestible energy intake from starches (Valberg, 2012). Ideally, forage sources for PSSM horses should also be analysed for non-structural carbohydrate content (Borgia *et al.*, 2011). If fat supplementation is provided to horses with PSSM, long chain fat sources are considered the most appropriate (Borgia *et al.*, 2010). For optimal clinical response, however, both dietary and exercise changes must be made, and improvement occurs gradually over a period of weeks (Valberg *et al.*, 2011).

Current recommendations for management of RER also still focus on manipulation of the ration and exercise regimes. It is recommended that ≤20% of the daily digestible energy intake is provided from starches for these horses (McKenzie and Firshman, 2009). Furthermore, affected horses should concurrently have a regimented exercise routine with rest periods no longer than 24 hours, since diet and rest appear to represent separate risk factors for the occurrence of clinical disease (McKenzie *et al.*, 2003; Valberg, 2012). Affected horses respond rapidly to management alterations with significant improvement demonstrated within one week of dietary changes commencing (McKenzie *et al.*, 2003).

Recommendations for managing type 2 PSSM have also revolved around careful management of exercise routines and adjustment of the ration, including fat supplementation (Valberg, 2012). However, in light of the re-categorisation of this disorder as MFM, appropriate management of for this disease is not clearly understood at this time. Arabian horses with MFM are commonly already consuming a low starch ration, and it is unclear what role dietary factors might play in this disorder (Wilberger *et al.*, 2015). Since periods of rest are also reported to be a strong triggering factor for episodes of disease in Arabian horses, a consistent exercise routine appears to be critical, and daily exercise is encouraged including up to the time of racing events. Veterinarians attending endurance races should be alert to early or subtle signs of rhabdomyolysis in Arabian horses, since affected horses can continue racing despite substantial subclinical rhabdomyolysis (Wilberger *et al.*, 2015). Competing endurance horses should be carefully assessed at veterinary checks, and riders encouraged to repeatedly evaluate their horse's urine colour and to pay attention to subtle gait abnormalities, delayed heart rate recovery, and other vague clinical signs. Although rapid evaluation of serum CK during competitive events is challenging, testing is recommended for any horse suspected of having clinical or subclinical rhabdomyolysis, and routine pre- and post-race evaluations of serum creatine kinase activity may be of value in the diagnosis and management of affected horses (Wilberger *et al.*, 2015). Given the current dearth of knowledge regarding the aetiology and pathophysiology of MFM, informed management recommendations for Warmblood horses are informed management recommendations for Warmblood horses are limited. However, suggested approaches have included strategically timed dietary amino acid supplementation and the institution of an exercise program focused on enhancing the musculature of the back and core.(Valberg *et al.*, in press).

Recommendations for managing HYPP in horses have not changed substantially recently, and the effect of blocking registration of homozygous individuals with the American Quarter Horse Association (since 2007) on the prevalence of this trait in the Quarter Horse population has yet to be determined (Mickelson and Valberg, 2015). Similar restrictions could potentially be recommended for horses homozygous for the *GYS1* mutation associated with PSSM, since these individuals are at risk of more severe clinical disease and also have greater potential to propagate their genetic profile (Mickelson and Valberg, 2015).

In regard to pharmaceutical agents, *in vitro* and *in vivo* clinical trials indicate that orally administered dantrolene sodium has efficacy for preventing rhabdomyolysis in Thoroughbred horses with RER (Edwards *et al.*, 2003; López *et al.*, 1995; McKenzie *et al.*, 2004). Furthermore dantrolene may be useful in hastening healing of muscle injuries (Flacco *et al.*, 1989). Dantrolene reduces the release of calcium from the sarcoplasmic reticulum of skeletal muscle cells, and prevents muscle contracture and necrosis in a variety of neuromuscular disorders (Krause *et al.*, 2004). Clinical trials have demonstrated that dantrolene can also prevent traumatic muscle damage in horses when it is administered prior to general anaesthesia (McKenzie *et al.*, 2004, 2015). However, dantrolene is lipophilic, and is best absorbed in horses that have not been feed deprived prior to administration, which may limit its utility for horses undergoing elective general anaesthesia or participating in track racing events (McKenzie *et al.*, 2010). As reported previously, dantrolene pre-medication of anaesthetised horses was reported to induce hyperkalemia and cardiac arrhythmias, and to decrease cardiac output, and it should be noted that the occurrence and significance of such effects have not yet been evaluated in exercising horses (McKenzie *et al.*, 2015). Furthermore, current drug testing withdrawal time recommendations are based on low doses of dantrolene administered after prolonged feed restriction, and are therefore potentially questionable (DiMaio Knych *et*

al., 2011). Nonetheless, dantrolene has been used commonly in racing Thoroughbreds in the United Kingdom; in the USA, some owners of Arabian endurance horses with MFM anecdotally report control of clinical signs by preemptive treatment with dantrolene sodium (McGowan *et al.*, 2002a). However the efficacy of this drug for control of MFM has not been studied, and due to the expense of this drug, some owners in the USA are utilising compounded formulations of unknown quality and stability.

Finally, a variety of rehabilitative therapies, including a range of physiotherapy and electrophysical methods, are progressively being employed to treat and manage musculoskeletal disorders in equine athletes (Kaneps, 2016; Schlachter and Lewis, 2016). Although specific recommendations have been published regarding the use of these modalities for different disorders, there is a dearth of scientific literature to confirm their efficacy or to determine appropriate protocols for their use in horses. Further investigation is needed to definitively determine their effectiveness in equine muscular disorders. Similar concerns exist in regard to regenerative medicine therapies, though equine induced pluripotent stem cells have been produced and it has been suggested that these might also have utility in the treatment of equine muscle injuries (Lee *et al.*, 2016). The flourishing interest in equine rehabilitation and the establishment of specialty colleges related to this field will hopefully provoke a concurrent increase in appropriately controlled scientific assessments of these progressively utilised modalities.

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