Equine vet. J., Suppl. **30** (1999) 458-462

Effect of diet on Thoroughbred horses with recurrent exertional rhabdomyolysis performing a standardised exercise test

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Keywords: horse; tying-up; fat; muscle; glycogen

Summary

Previous studies have associated recurrent exertional rhabdomyolysis (RER) with a diet high in soluble carbohydrate (CHO). The purpose of this study was to investigate the effect of 3 diets on clinical and metabolic parameters in 5 Thoroughbred horses with RER and 3 healthy Thoroughbreds performing a standardised exercise test (SET). Two diets were formulated to meet energy requirements for the amount of exercise being performed in the form of CHO or fat (21.4 Mcal DE/day). The third diet was formulated to provide 135% of the DE of the other 2 diets in the form of an excessive amount of carbohydrate (28.8 Mcal DE/day). Diets were fed in a crossover design for 3 week blocks and then horses performed a near maximal SET. Changes in heart rate (HR), plasma lactate, plasma glucose, total plasma solids, packed cell volume (PCV), muscle lactate and muscle glycogen concentration were measured immediately prior to, during, and 5 min after exercise. Serum creatine kinase (CK) activity was measured prior to and 4 h post SET. A 2-way ANOVA was used to examine the effect of group and dietary treatment. When dietary treatments were compared, horses fed the high-CHO diet had a mean pre-SET PCV and pre-SET HR that was higher than horses fed the fat diet ($P = 0.06$ and $P = 0.07$, respectively). Pre-SET heart rates were highest in RER horses consuming the high-CHO diet compared to RER horses consuming the low-CHO and fat diets ($P = 0.02$). Horses with RER had 4 h post SET CK activity greater than 400 u/l in 7/14 (50%) measurements compared to control horses which had CK activity greater than 400 u/l in 2/7 (29%) measurements. This study did not demonstrate a significant effect of diet on rhabdomyolysis, indicated by CK activity, or on the metabolic response to exercise. However, diet may have a calming effect on Thoroughbred horses with RER as manifested by decreased pre-exercise heart rates and decreased pre-exercise PCV in horses fed the fat diet.

Introduction

Exertional rhabdomyolysis is the most common equine myopathy (Freestone and Carlson 1991). Early research by Carlstrom (1932) implicated a high-CHO diet, glycogen storage and subsequent lactic acidosis in the pathogenesis of exertional rhabdomyolysis in draught horses. This hypothesis was subsequently applied to all horses with exertional rhabdomyolysis (McLean 1973). More recent research has described several forms of chronic exertional rhabdomyolysis including polysaccharide storage myopathy (PSSM) affecting Quarter Horses and draught horses and recurrent exertional rhabdomyolysis (RER) which affects Thoroughbreds and Standardbreds (Beech *et al.* 1993; Valberg 1996; Valentine *et al.* 1997a; Lentz *et al.* 1999). However, neither disorder has abnormally high muscle lactate concentrations that correlate with rhabdomyolysis post exercise (Valberg *et al.* 1993, 1999a). High muscle glycogen concentrations and accumulation of abnormal polysaccharide have been reported in Quarter Horses and draught horses with PSSM (Valentine 1997a; Valberg *et al.* 1999a). Glucose tolerance tests in Quarter Horses with PSSM suggests that increased glycogen accumulation results from increased glucose uptake by muscle (De La Corte *et al.* 1999). Therefore, it is recommended that horses with PSSM be placed on diets low in carbohydrate and high in fat (Valberg 1996; Valentine 1997b).

Recurrent exertional rhabdomyolysis occurs in approximately 5% of racing Thoroughbreds, making it an important source of economic loss (Jeffcott *et al.* 1982; Rossdale *et al.* 1985; Sorum *et al.* 1997). The aetiology of the condition is unknown, although recent evidence suggests that in many cases RER in Thoroughbreds is a heritable, stress-related disorder of muscle contractility (Lentz *et al.* 1999; MacLeay *et al.* 1999a). Muscle glycogen concentrations are often normal in Thoroughbreds with RER. However, some horses with RER have been found to have moderately elevated muscle glycogen concentrations compared to healthy horses (Valberg *et al.* 1998). Thoroughbred horses with RER have been found to have normal glucose tolerance tests (Valberg *et al.* 1998). Although muscle glycogen concentrations vary in Thoroughbreds with RER anecdotal reports favour the use of low-CHO/high-fat diets in decreasing the frequency of episodes of rhabdomyolysis in Thoroughbred horses with RER. A common recommendation for horses with RER is to decrease the total soluble CHO portion of the diet or replace calories supplied as CHO with fat (Farrow *et al.* 1976; Valberg 1996). The purpose of this study was to determine the effect of fat and excessive CHO intake on the metabolic response to a near-maximal SET in Thoroughbred horses with and without RER.

TABLE 1: Daily intake of nonstructural carbohydrates (NSC), fat, neutral detergent fibre (NDF) and protein for the 3 diets, including the % digestible energy contributed by each fraction

	Diet 1: Low carbohydrate			Diet 2: High carbohydrate			Diet 3: Fat		
Fraction	Composition as fed %	Daily intake g/day	Energy contribution % of total	Composition as fed %	Daily intake g/day	Energy contribution % of total	Composition as fed %	Daily intake g/day	Energy contribution % of total
NSC	33.6	2986	47	38.6	4244	53	24.8	2158	34
Fat	2.6	235	8	2.8	303	8	7.1	619	20
NDF	30.4	2705	18	27.6	3036	16	31.2	2714	18
Protein	14.9	1326	27	13.6	1496	23	16.3	1421	28

Materials and methods

Horses

Five female Thoroughbred horses (age 4, 5, 6, 10, 13 years) with RER and 3 healthy Thoroughbreds (2 mares age 4 and 13 years, and one 12-year-old gelding) were used. Horses weighed 480–585 kg. All horses were housed in an accredited facility and were cared for according to the principles outlined in the National Institute of Health Guide for the care and use of laboratory animals. Recurrent exertional rhabdomyolysis was diagnosed based on the presence of all of the following: 1) historical episodes of exercise induced muscle pain and stiffness, 2) intermittent elevations in serum CK of greater than 1000 u/l, 3) Changes in muscle histopathology including increased numbers of central nuclei in type 2A and 2B fibres and absence of abnormal polysaccharide on PAS stain and 4) abnormal potassium, caffeine and halothane contracture studies (Lentz *et al.* 1999; Valberg *et al.* 1999b).

Control horses had no histories of rhabdomyolysis, normal muscle histology and normal muscle contracture tests. All horses were exercised on a treadmill 4 or 5 days per week for 30 min/day at a walk, trot, canter or gallop (11 m/s) for at least 6 weeks prior to the beginning of the study to establish a comparable level of fitness. During this period horses were fed free choice alfalfa hay and 2.5 kg of 10% protein sweet feed/day.

Diet

Horses were rotated between 3 diets (low-CHO, high-CHO, fat) for a period of 3 weeks on each diet (Table 1). The first diet was assigned randomly and the following 2 diets were assigned in a crossover design such that all 3 diets were fed first in at least 2 horses. The fat and low-CHO diets were formulated to meet the caloric needs of horses performing this level of exercise (21.4 Mcal DE/day including forage) and the high-carbohydrate diet was formulated to provide 135% of the calories of the other 2 diets (28.8 Mcal DE/day including forage). The low- and high-CHO diets were composed of a molasses-supplemented grain (2.5 kg and 4.6 kg/day, respectively). The fat diet was composed of 2.3 kg/day of a calcium-balanced rice bran. A protein, vitamin and mineral supplement (0.7 kg/day) was provided with each diet. Forage was provided as 5.7 kg/day of an alfalfa/timothy hay cube. Forage and grain were divided into 2 equal feedings fed at 12 h intervals (morning and evening) 7 days/week. The protein supplement was fed entirely in the evening meal. The morning meal was fed 1 or 2 h before performing the SET.

Horses performed identical exercise protocols Monday to Friday for 3 weeks. On Mondays and Fridays horses performed a warm-up protocol comprised of 15 min walk and trot and then galloped for 2 min at 11 m/s on a 6% slope. On Tuesdays and Thursdays horses performed the warm-up protocol followed by 3 x 2 min intervals canter at 9 m/s interspersed with 2 min of walking. On Wednesdays horses trotted for 30 min at 4.5 m/s. The SET was performed on the last Friday of the third week. Horses were moved onto the next diet the day after each SET was performed. All horses were weighed prior to beginning each SET.

Standardised exercise test (SET)

The SET consisted of a stepwise test with peak heart rates of at least 200 beats/min. Horses walked at 1.9 m/s on the level for 2 min. The treadmill was inclined to 6% and horses walked for 2 min more. Horses then trotted at 4.5 m/s for 2 min, cantered at 7 m/s, 10 m/s and 11 m/s each for 2 min. After completing the SET horses stood on the treadmill for a 5 min cool down period. Heart rates were measured with the use of the Equistat heart rate monitor (model HR-8AE)[1]. Blood samples were obtained via a jugular catheter into heparinised syringes and heart rates recorded while the horse stood on the treadmill before testing began, during the last 30 s at each speed and 5 min after the conclusion of the test. A serum sample was collected before and 4 h after exercise for measurement of CK activity (Beckman CX4 analyser)[2]. Packed cell volume (microhaematocrit tube centrifugation), total plasma solids (refractometer), plasma lactate and plasma glucose concentrations (YSI 2300 STAT L-Lactate and glucose analyser)[3], were measured on all blood samples taken except the 4 h post exercise sample. Plasma for lactate and glucose analysis was frozen at -20°C until analysed.

Muscle samples

A middle gluteal muscle biopsy was obtained prior to and immediately upon completion of the SET according to Lindholm and Piehl (1974) from a standardised site (Valberg 1996). Muscle samples were frozen immediately in liquid nitrogen and stored at -80°C until analysed. Muscle samples were freeze dried and analysed for glycogen and lactate by fluorometric analysis according to Lowry and Passonneau (1973).

Statistics

A 2-way analysis of variance and Tukey's comparison of means was performed using Statistix version 1.0 Software[4]. Comparisons were made between the independent variables of group (RER/control) and dietary treatment to HR, PCV, TP, CK, plasma lactate, plasma glucose, muscle lactate and muscle glycogen concentration. In addition, change in CK, change in

TABLE 2: Mean and range of parameters before and immediately after a standardised exercise test (SET) in Thoroughbred horses with and without recurrent exertional rhabdomyolysis (RER)

	Low-carbohydrate diet mean		High-carbohydrate diet mean		Fat diet mean	
	RER	Control	RER	Control	RER	Control
Pre-SET HR (beats/min)	40 (33–49)	39 (37–40)	50 (44–60)	42 (40–46)	39 (35–40)	40 (31–49)
Post SET HR	190 (150–212)	202 (194–210)	202 (190–220)	201 (193–209)	197 (180–215)	203 (199–206)
Pre PCV %	41 (37–45)	43 (42–44)	41 (36–44)	44 (38–48)	40 (30–48)	35 (33–36)
Post PCV	63 (57–67)	60 (57–62)	62 (59–64)	61 (60–62)	62 (55–69)	64 (59–69)
Pre [pl. lact.] (mmol/l)	0.80 (0.5–1.1)	0.55 (0.4–0.7)	0.75 (0.6–0.9)	0.87 (0.5–1.5)	0.74 (0.6–1)	0.65 (0.6–0.7)
Post [pl. lact.]	9.06 (7.7–12)	20.30 (9.2–31.4)	10.78 (7.8–13.7)	16.27 (10.1–19.4)	9.27 (5.4–13.4)	20.40 (5.6–35.2)
Pre CK (u/l)	189 (105–435)	207 (117–296)	365 (124–678)	606 (125–1496)	337 (72–1093)	146 (131–161)
Post CK	361 (217–655)	360 (168–551)	457 (150–755)	824 (174–1927)	871 (167–3000)	235 (231–239)
Pre [m. glyc.] (mmol/kg DW)	493 (408–538)	524 (508–540)	559 (470–666)	455 (438–469)	473 (427–519)	510 (465–566)
Post [m. glyc.]	408 (358–479)	437 (378–495)	466 (397–579)	383 (350–413)	409 (356–465)	436 (401–470)
Pre [m. lact.] (mmol/kg DW)	31 (21–44)	22 (21–24)	30 (19–38)	35 (31–39)	31 (25–35)	20 (17–22)
Post [m. lact.]	66 (61–71)	142 (71–214)	64 (51–75)	98 (58–134)	86 (41–119)	62 (48–77)

CK = creatine kinase, beats/min = beats per min, DW = dry weight, HR = heart rate, lact. = lactate, m. = muscle, PCV = packed cell volume, pl. = plasma.

muscle lactate concentration and change in muscle glycogen concentration were also analysed. The interaction between group and diet was used as the error term. A Tukey's comparison of means was used due to the unequal number of SET's in treatment groups. Results are reported in the text as mean ± s.e. and statistical significance set at $P<0.05$ with trends indicated by $P<0.10$.

Results

One control horse performed the pre-study and high-grain SETs but was unable to complete the study due to lameness unrelated to rhabdomyolysis. One RER horse failed to complete the high-grain SET due to treadmill breakdown. When fed the low-CHO or fat diets horses lost mean 1.2 ± 1.6% or 1.1 ± 1.6% of bwt, respectively. Horses gained a mean 2.4 ± 0.3% their bwt while consuming the high-CHO diet. These values were not significantly different from one another. Mean values for blood glucose, TP, PCV, HR, plasma lactate, creatine kinase activity, muscle glycogen, and muscle lactate, broken down by diet for RER and control horses are shown in Table 2.

Blood glucose, TP, PCV and HR

When dietary treatments and affected/control groups were compared, there were no significant differences with respect to TP values and plasma glucose concentrations for before, during and after the SET.

There was no difference between RER and control horses with respect to pre-SET PCV and there was no difference between groups or dietary treatments for PCV values during and after the SET. When dietary treatments were compared, mean pre-SET PCV for horses consuming the high-grain diet tended to be higher, 42.3 ± 1.6 % compared to those consuming the fat diet (38.3 ± 2.3%, $P = 0.06$).

No differences in HR taken during and after the SET were found between diets and between groups. Both RER and control horses tended to have higher pre-SET HRs when fed the high CHO diet compared to both the low-CHO and fat diets ($P = 0.07$). Overall, mean pre-SET HR was 46 (3 beats/min for the high-CHO diet, 40 ± 2 beats/min for the low-CHO diet, and 39 ± 2 beats/min for the fat diet. Mean pre-SET HR for RER horses consuming the high-CHO diet was significantly higher (50 ± 4 beats/min) than when the RER horses consumed the fat or low-CHO diets ($P = 0.02$). The trend was similar for control horses fed the high-CHO diet.

Blood lactate, muscle lactate and muscle glycogen

When dietary treatments and affected/control groups were compared, there was no significant difference with respect to plasma lactate concentrations taken before and during the SET. In addition, there was no dietary effect on post SET plasma lactate concentration. One control horse had a significantly higher mean post SET plasma lactate concentration compared to all other horses ($P<0.05$).

There was no statistically significant difference for post SET muscle lactate concentrations between groups or dietary treatments. In RER horses, there was no dietary effect on pre-SET muscle lactate concentration. However, in the control horses, feeding the high-carbohydrate diet was statistically associated with increased pre-SET muscle lactate concentration compared to the low-CHO and fat diets ($P = 0.02$).

Statistically significant differences in pre-SET muscle glycogen concentrations were not seen when groups and dietary treatments were analysed. However, there was a trend for higher glycogen concentrations in all horses when fed the high-CHO diet (514 ± 34 mmol/kg DW) and lower glycogen concentrations when fed the fat diet (484 ± 17 mmol/kg DW) compared to the low-CHO diet (501 ± 17 mmol/kg DW). In RER horses, muscle glycogen concentrations were 13% higher when the high-CHO diet was fed compared to the low-CHO diet and 18% higher than muscle glycogen concentrations in RER horses fed the fat diet. Glycogen utilisation during the SET was not different between RER and control horses and was unaffected by dietary treatment.

Effect of diet on serum CK activity

There was no statistically significant effect of group or dietary treatment on pre-, post or change in CK activity. Pre-exercise CK activity was within the normal range (<400 u/l) for all control horses on all diets with the exception of one filly consuming the high-CHO diet (CK = 1496 u/l, 1/7 [14%]

measurements). Pre-exercise CK activity was greater than 400 u/l in RER horses in 3/14 (21.4%) measurements (CK = 435–1093 u/l). The 3 measurements were taken from different horses each consuming a different diet. Four hours post SET CK activity was greater than 400 u/l in 7/14 (50%, range 407–3000 u/l) measurements for RER horses and 2/7 (28.6%, 551 and 1927 u/l) measurements in control horses. Post SET CK for RER horses consuming the high-CHO diet was greater than 400 u/l in 3/4 horses (75%).

Discussion

The results of this study show very little effect of the 3 diets on the cardiovascular and metabolic responses to exercise. Measurements for HR, TP, plasma glucose, muscle lactate and glycogen utilisation were similar between groups and dietary treatments during and after the SET. Therefore, we encountered neither a beneficial nor an adverse effect on these parameters as a result of training for 3 weeks on the diets formulated for this study.

Muscle glycogen concentrations were slightly higher in RER horses fed the high-CHO diet compared to the low-CHO and fat diets. However, no statistically significant differences in muscle glycogen concentrations were observed between dietary treatments or between groups. This may have been due to the small number of horses used in this study and/or the length of time each diet was fed. Moderate increases in resting muscle glycogen concentration in horses receiving supplemental CHOs or feed grade animal fats or vegetable oils has been previously reported (Pagan *et al.* 1987; Meyers *et al.* 1989; Essén-Gustavsson *et al.* 1991; Julen *et al.* 1995; Orme *et al.* 1997). In a previous study, Julen *et al.* (1995) found that horses adapted readily to fat-supplemented diets within 28 days. However, our results suggest that feeding 2.3 kg rice bran per day for 3 weeks, as a source of fat, to Thoroughbred horses will not significantly affect muscle glycogen concentrations.

Harris and Snow (1988) examined Thoroughbred horses, performing a near-maximal SET, and demonstrated little individual variation but marked differences between individuals in venous lactate concentrations. In the current study, we observed this marked variation in plasma and muscle lactate concentration between horses with little variation in individual horses as well. The significant difference between groups in post SET plasma lactate concentrations was due to a single control horse compared to all other horses in the trial. The small number of horses in this study and the marked individual variations observed in plasma and muscle lactate concentration make interpretation of these findings difficult.

In the Thoroughbred horses with RER there was no positive correlation between plasma lactate or muscle lactate and serum CK, or signs of rhabdomyolysis. This was similar to previous studies in Standardbred horses (Valberg *et al.* 1993). Horses with RER showed no clinical signs of rhabdomyolysis throughout the study and increases in serum CK activity were intermittent. However, post exercise peak CK activity above the reference range did occur more frequently in RER horses compared to control horses and mean increase in CK activity was usually higher in RER horses compared to controls (Table 2). The frequency of episodes of rhabdomyolysis varies significantly among susceptible horses and the onset of an episode is probably influenced by many environmental and metabolic factors. This study examined the effect of diet on performance of a single near maximal exercise test designed to achieve near-maximal speeds. These results support preliminary results from an epidemiological study that found horses with RER rarely have episodes of rhabdomyolysis when racing but often do when training (MacLeay *et al.* 1999b). Studying CK activity following one near-maximal exercise test may not be the best way to evaluate dietary influences on rhabdomyolysis. The effect of diet on the expression of RER in horses performing daily exercise at varying exercise intensities will be examined in a future study.

One effect of the high-CHO diet measured subjectively was the increased nervousness and excitability of horses consuming the high-CHO diet compared to the low-CHO and fat diets. Horses on the high-CHO diet were subjectively more reactive in their stalls, difficult for one person to catch and difficult to lead from the barn to the treadmill. Conversely, when fed the fat diet the same horses were regarded as more docile and willing to exercise. These findings follow the observations of Holland *et al.* (1996) where the authors demonstrated that horses fed diets high in fat were more tractable than horses fed control diets.

Increased excitement or anticipation of exercise were evaluated objectively by measuring pre-exercise HR and PCV while the horses stood on the treadmill immediately before commencing the SET. Mean pre-exercise PCV in our study was highest in both RER and control horses consuming the high-CHO diet. In addition, RER horses had significantly higher immediate pre-exercise heart rates than control horses and pre-exercise heart rates were highest in RER horses consuming the high-CHO diet. Epidemiological studies have found that female Thoroughbred racehorses are more nervous than males and that female Thoroughbreds with RER are described as nervous or very nervous twice as often as sex-matched healthy controls (Kusunose *et al.* 1997; MacLeay *et al.* 1999b). Therefore, a potential benefit of providing calories from a fat source in place of grain may be increased tractability while consuming the same amount of calories. Whether the increased activity seen in horses consuming the high-grain diet was due to increased caloric intake or increased CHO intake needs to be investigated. However, Pagan *et al.* (1987) reported similar increased excitability in horses consuming a high-CHO diet compared to an isocaloric low-CHO diet.

Recurrent exertional rhabdomyolysis in many Thoroughbreds is probably an heritable condition characterised by abnormal intracellular calcium regulation (Lentz *et al.* 1999; MacLeay *et al.* 1999a). An association between anxiety or nervousness and the onset of episodes has been observed in Thoroughbred racehorses with RER as well as other disorders of intracellular calcium regulation such as malignant hyperthermia (Mickelson and Louis 1996; MacLeay *et al.* 1999b). The pathophysiological mechanisms involved in the clinical manifestation of rhabdomyolysis in response to a high-stress environment is unknown. Successful management of horses with RER should necessarily include strategies to minimise stress and excitability. Such management changes may include altering the diet to decrease CHO intake and therefore influence the expression of the disorder by decreasing excitability. In this study, decreased excitability could have been reflected by the decrease in pre-SET heart rates and packed cell volume in horses fed the fat diet compared to the high-CHO diet. In RER-susceptible Thoroughbred racehorses this may result in a decrease in clinical episodes of rhabdomyolysis. The intermittent nature of rhabdomyolysis in RER makes it difficult to assess the effect of diet on the development of rhabdomyolysis using a single exercise test per diet. To address this difficulty, the effect of diet on the development of rhabdomyolysis will be examined by analysing data from daily exercise at differing exercise intensities in a future study.

Acknowledgements

The authors thank the Minnesota Racing Commission and the Minnesota Research Center for financial support.

Manufacturers' addresses

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[2]Beckman ICS, Brea, California, USA.
[3]Yellow Springs Instrument Co., Yellow Springs, Ohio, USA.
[4]Analytical Software,Tallahassee, Florida, USA.

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