Equine Metabolic Syndrome

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KEYWORDS

• Obesity • Regional adiposity • Hyperinsulinemia
• Insulin resistance • Laminitis

Veterinarians have long recognized that obese horses and ponies are prone to laminitis, but the concept of an equine metabolic syndrome (EMS) was first proposed by Johnson[1] in 2002. This concept has developed over time, and EMS was recently described in a consensus statement released by the American College of Veterinary Internal Medicine.[2] In human medicine, metabolic syndrome (MetS) refers to a set of risk factors that predict the risk of cardiovascular disease,[3] including obesity, glucose intolerance and insulin resistance (IR), dyslipidemia, microalbuminuria, and hypertension. Associated conditions in humans include nonalcoholic fatty liver disease and polycystic ovary syndrome. EMS shares some of the features of MetS, including obesity, IR, and dyslipidemia, but differs in that laminitis is the primary disease of interest.

COMPONENTS OF THE SYNDROME

EMS is not a specific disease entity, but rather a clinical syndrome associated with laminitis.[4,5] Increased adiposity, hyperinsulinemia, and IR are the 3 principal components of this syndrome, and it is difficult to separate these factors from one another. Hyperinsulinemia is detected in most insulin resistant horses and affected animals are usually obese or exhibit regional adiposity (**Fig. 1**). One or all of these factors may determine laminitis susceptibility, but it is also conceivable that another, as yet unidentified, factor predisposes horses with EMS to laminitis. Other components of EMS include dyslipidemia,[4–6] altered blood adipokine concentrations,[5,7,8] systemic inflammation,[9] and seasonal arterial hypertension.[10] In contrast to MetS in humans, atherosclerosis and coronary heart disease are not detected in horses with EMS, and this may be explained by the herbivorous diet of horses or lipoprotein composition

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Fig. 1. A 7-year-old Morgan horse mixed breed mare with physical characteristics of equine metabolic syndrome.

of equine blood. Most circulating cholesterol is carried within high-density lipoproteins in horses, rather than low-density lipoproteins, which are atherogenic.[11]

BREED PREDISPOSITION

EMS occurs most commonly in pony breeds, Morgan horses, Paso Finos, Arabians, Saddlebreds, Quarter horses, and Tennessee Walking horses. Most horses and ponies with EMS are obese, and owners often describe them as "easy keepers." Environmental issues such as overfeeding and lack of exercise contribute to obesity, and these problems are increasing with modern management practices.

CLINICAL PRESENTATION

Laminitis

Horses and ponies with EMS are predisposed to laminitis, so this is the most common presenting complaint. Laminitis typically develops after animals have been grazing on pasture, which is referred to as pasture-associated laminitis.[12] Episodes of laminitis often occur after heavy rains and abundant sunlight, when grasses have been growing rapidly and accumulating water-soluble carbohydrates (WSC) through increased photosynthesis.[13] Grazing on rapidly growing pastures increases total energy intake and promotes obesity, while also increasing WSC consumption. Resting insulin concentrations increase as a result, and this alters proxy measures of insulin sensitivity and pancreatic output.[4,5] However, proxy measures used for blood samples have been collected under fed conditions in previous studies, so it is difficult to determine whether insulin sensitivity per se progressively decreases in response to pasture grazing. This distinction is an important one because laminitis has been experimentally induced in ponies and horses by infusing insulin intravenously, suggesting that hyperinsulinemia is the trigger for disease.[14,15] One challenge for researchers in the future is to conduct studies in which the effects of obesity, IR, and hyperinsulinemia on laminitis development are evaluated independently.

Pasture grazing also raises the risk of intestinal carbohydrate overload, particularly when animals are moved onto new pastures without gradual transition.[12] In these situations, the amount of WSC entering the intestinal tract exceeds the digestive and absorptive capacities of the small intestine and increases the amount of substrate

available for fermentation within the large intestine. Increased fermentation raises lactic acid concentrations, lowers pH, and increases mucosal permeability.[16] Movement of gut-derived factors including exotoxins, endotoxins, and vasoactive amines into the circulation induces a systemic inflammatory response and activates platelets.[17] Evidence for an intestinal trigger for pasture-associated laminitis comes from studies in which oligofructose has been administered to horses as a model for carbohydrate overload on pasture. Treated horses exhibit clinical signs consistent with a systemic inflammatory response, followed by laminitis.[18–20]

Laminitis is typically thought of as a catastrophic event causing severe lameness, but a milder form of laminitis is often detected in horses and ponies with EMS. Divergent growth rings (founder lines) are sometimes recognized in horses that are walking soundly, indicating that hoof growth has been disrupted by a previous laminitis episode (**Fig. 2**). A growth ring is considered divergent when the distance to the coronary band is shorter at the dorsum than the heel. These findings suggest that horses develop laminitis that goes unnoticed by the owner, particularly when animals are kept on pasture. A full diagnostic evaluation should therefore include lateral radiographs of the feet and placement of hoof testers. Mild lameness associated with laminitis can sometimes be detected by tightly circling the horse on a hard surface.

Complications of Hospitalization

There are anecdotal reports of horses and ponies with EMS showing greater susceptibility to laminitis triggered by grain overload, retained fetal membranes, and colitis. It is therefore important to recognize the EMS phenotype and alert owners to the potential risk of laminitis. Obese horses are also susceptible to colic caused by lipomas. A pedunculated lipoma can lead to strangulation of the small intestine and moderate to severe colic, accompanied by intestinal distension and reflux.

Problems with IR are sometimes recognized for the first time when hypertriglyceridemia develops in hospitalized patients that enter negative energy balance. Insulin-resistant horses mobilize lipids more readily and are more susceptible to equine hyperlipemia.[11] Hyperglycemia and glucosuria may also be detected in affected horses when dextrose is administered intravenously to provide partial parenteral nutrition. Exogenous insulin is often required in these cases to maintain plasma glucose concentrations below renal threshold while dextrose is administered. Of interest, there

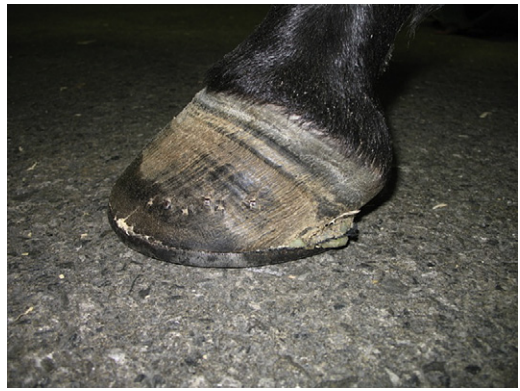

Fig. 2. Divergent growth rings (founder lines) indicating previous laminitis.

have been no reports of laminitis developing as a result of intravenous insulin infusion to manage hyperglycemia.

Obesity and Regional Adiposity

As more owners and veterinarians have become aware of EMS, obesity and regional adiposity are increasingly identified as abnormal states during routine health examinations. Severely affected horses have a body condition score (BCS) of 8 or 9 on the 1 (poor) to 9 (extremely fat) scale developed by Henneke and colleagues[21] and marked expansion of the neck crest, which may fall to one side. Enlargement of adipose tissues within the neck region is a common manifestation of regional adiposity and is commonly referred to as a cresty neck (**Fig. 3**) Carter and colleagues[22] created a scoring system to assess horses with this form of regional adiposity using a 0 to 5 range, and scores of 3 or more are often detected in horses or ponies with EMS (**Fig. 4**). The description provided for a score of 3 is "Crest enlarged and thickened, so fat is deposited more heavily in middle of the neck than toward poll and withers, giving a mounded appearance. Crest fills cupped hand and begins losing side-to-side flexibility." Neck circumference can also be measured by dividing the distance along a line from the poll to the cranial aspect of the withers (x) by 4 and measuring the circumference of the neck at 3 equidistant points (0.25x, 0.50x, and 0.75x). These measurements can be used to assess progress after management plans are implemented.

Preputial or Mammary Gland Swelling

Obese geldings affected by EMS sometimes present with the complaint of preputial swelling (**Fig. 5**), with insect bites or trauma suspected. However, further examination reveals adipose tissue expansion and edema secondary to reduced lymphatic return. Owners should be questioned about the body condition of their horse and whether obesity has developed in the past few months. Because edema can be a component of this preputial swelling, it is exacerbated by stall confinement and addressed by increasing exercise. Horses with this problem respond well to weight loss, indicating that expanded adipose tissue is the primary problem. Mares with EMS sometimes present with adipose tissue expansion in the mammary gland region.

Fig. 3. A horse exhibiting regional adiposity in the form a pronounced neck crest, which is referred to as a cresty neck.

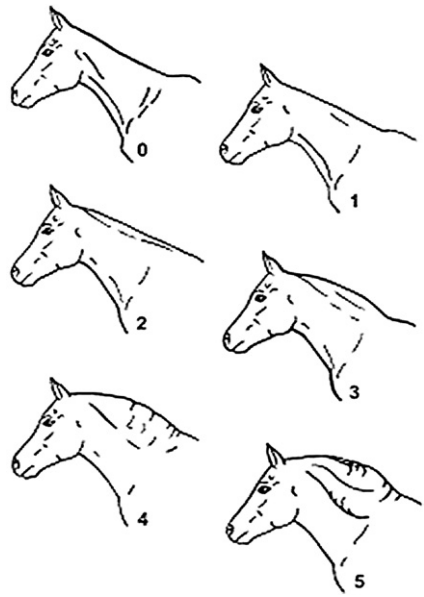

Fig. 4. Crest neck scoring system. (*Reprinted from* Carter RA, Geor RJ, Burton SW, et al. Apparent adiposity assessed by standardised scoring systems and morphometric measurements in horses and ponies. Vet J 2009;179:204; with permission.)

PATHOPHYSIOLOGY

Predisposition

Some horses and ponies appear to be genetically predisposed to EMS, and this is the focus of ongoing study at the University of Minnesota (www.cvm.umn.edu/equinegenetics/ems). There are numerous anecdotal reports of EMS in related horses and ponies, and Treiber and colleagues[4] detected a dominant inheritance pattern for laminitis in ponies with EMS. Many animals with EMS appear to require fewer calories to maintain body weight, indicating enhanced metabolic efficiency. Genetic

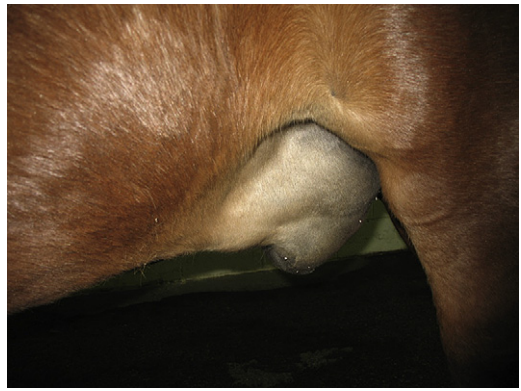

Fig. 5. Adipose tissue expansion around the prepuce of a 16-year-old Tennessee Walking horse gelding.

predisposition to obesity may involve specific gene mutations, and the concept of "thrifty genes" warrants consideration.[23] This theory has been applied to humans, and focuses on the concept of famine conditions leading to selection of metabolic genes that improve metabolic efficiency, promote obesity, and increase appetite when food is plentiful. One candidate gene is the melanocortin-4 receptor (MC4R), which regulates feed intake, insulin sensitivity, and adiposity, and results of a preliminary study indicate that a single nucleotide polymorphism exists within the coding region of this gene in horses.[24]

Fetal programming might also affect metabolic status because fetal birth weight has been inversely associated with the risk of developing type 2 diabetes mellitus in humans.[25] This feature can be described as a "thrifty phenotype" that is determined by environment rather than genetics.[23] For example, the increased risk of type 2 diabetes mellitus has been attributed to inadequate pancreatic development caused by nutrient deprivation during pregnancy.[25] With respect to obesity, some reports indicate that in utero nutrient deficiency increases the incidence of this problem, whereas others demonstrate a positive association between birth weight and body mass index later in life.[24] Fetal programming has been examined in horses. Ousey and colleagues[26] fed mares to maintain moderate or high BCSs during pregnancy, but all horses inadvertently lost approximately 10% of body mass at mid-gestation as a result of *Streptococcus equi* infection. When intravenous glucose tests were performed in foals at 2 to 4 days of age, insulin concentrations were higher in foals from moderate BCS mares. These results suggest that acute nutrient restriction at mid-gestation affected foals in utero and altered β-cell responsiveness or insulin sensitivity. Feeding mares a high starch diet during pregnancy has also been shown to affect glucose concentrations and insulin sensitivity in preweaned foals.[27] A trend toward lower insulin sensitivity was detected in foals at 160 days of age. Further studies are therefore required to determine whether nutrient deficiency or excess during gestation contribute to the development of EMS. It is possible that epigenetics plays a role in EMS if environmental conditions induce heritable changes in gene expression without altering the DNA sequence.[3] Epigenetic effects are mediated by alterations in DNA methylation or histone configuration, and might explain why in utero conditions during one pregnancy affect subsequent generations.

Hyperinsulinemia

It is assumed that hyperinsulinemia results from increased pancreatic insulin secretion in response to reduced insulin sensitivity, and this is referred to as compensated insulin resistance.[28] Values for insulin sensitivity and the acute insulin response to glucose (AIRg) provide evidence of compensated IR in insulin-resistant horses and ponies. These values are estimated from minimal model analysis of frequently-sampled intravenous glucose tolerance test (FSIGTT) data, with AIRg representing pancreatic insulin secretion. Treiber and colleagues[29] reported higher AIRg values in horses and ponies with lower insulin sensitivity, and Carter and colleagues[30] demonstrated that mean AIRg increased by 408% as insulin sensitivity decreased by 71% when obesity was induced in Arabian geldings. In contrast, uncompensated insulin resistance refers to inadequate insulin secretion in response to IR, with higher glucose concentrations detected. This situation has been described in clinically laminitic ponies, and should be suspected whenever hyperglycemia is detected in an animal with the physical characteristics of EMS.[4] A dynamic test is recommended in these cases because hyperinsulinemia may be absent. Diabetes mellitus also occurs in horses and is characterized by persistent hyperglycemia, with glucosuria detected in some cases. This condition may be more common than previously thought, and

has been detected in horses with pituitary pars intermedia dysfunction.[31] Inadequate pancreatic insulin secretion results in hyperglycemia with concurrent IR in some, but not all, cases.

Recent evidence suggests that higher blood insulin concentrations also result from reduced hepatic insulin clearance.[32] Pancreatic insulin secretion can be assessed by measuring serum connecting peptide (C-peptide) concentrations because this molecule is released with insulin as the hormone is secreted. Approximately 70% of insulin secreted by the pancreas is cleared by the liver, whereas C-peptide remains in circulation.[32] The C-peptide to insulin ratio therefore reflects hepatic insulin clearance. Obese horses have high insulin and C-peptide concentrations, yet lower C-peptide to insulin ratios, indicating both increased insulin secretion and reduced hepatic clearance.[32]

Hepatic Insulin Resistance

Higher plasma γ-glutamyl transferase (GGT) and aspartate aminotransferase (AST) activities are detected in some horses with EMS, and lipid accumulation within hepatocytes is a common postmortem finding. This feature suggests that hepatic lipidosis develops in some horses with EMS in the same way that nonalcoholic fatty liver syndrome has been associated with MetS in humans.[3] Reduced insulin clearance by the liver in horses with EMS is a manifestation of hepatic IR. This problem reflects the impact of obesity on liver function and includes upregulation of inflammatory pathways.[33] Results of a preliminary study indicate that Toll-like receptor pathways are upregulated in the liver of obese insulin-resistant horses.[34] Impaired hepatic function might also increase the risk of laminitis by reducing the clearance of gut-derived triggers for laminitis or altering the metabolism of dietary carbohydrates.

Peripheral Insulin Resistance

Insulin resistance is defined as a reduction in the action of insulin on target tissues.[35] Normal actions of insulin include inhibition of gluconeogenesis and lipolysis and stimulation of glycogen synthesis.[33] Mechanisms of IR include defects in the insulin receptor, insulin signaling pathways, or glucose transporter 4 (GLUT4) synthesis, translocation, or function. One important action of insulin is to stimulate glucose transport into cells, and this occurs rapidly as GLUT4 proteins translocate to cell membranes. Vesicles containing preformed GLUT4 are present within the cytoplasm, and transporters move to the plasma membrane after activation by the insulin signaling cascade. Results of a recent study indicate that GLUT4 translocation is impaired in insulin-resistant horses. Waller and colleagues[36] demonstrated that GLUT4 translocation to the cell surface is significantly reduced in skeletal muscle from insulin-resistant horses, despite normal protein abundance. Results of this preliminary study provide the first information regarding mechanisms of IR in horses.

Obesity

Obesity develops as animals consume more energy than they expend. Studies have not been performed to measure metabolic efficiency or compare rates of weight gain among different breeds of horse, but increased awareness of EMS has led clinicians to recognize that some horses and ponies develop obesity more readily, and this problem is difficult to reverse in the same animals. When obesity has been induced in horses, the breed of horse has affected outcomes. Quinn and colleagues[37] failed to detect a decrease in insulin sensitivity associated with weight gain in Thoroughbred geldings whereas Carter and colleagues[30] induced IR in Arabian geldings by providing 200% of daily digestible energy requirement for 16 weeks. Body weight increased by

20% and insulin sensitivity decreased by 71% in the latter study as obesity was induced. These findings suggest that obesity has a greater impact on insulin sensitivity in certain animals, which corresponds with clinical observations that some obese horses are insulin resistant whereas others have normal insulin sensitivity. There is also evidence that obesity is more difficult to reverse in individual animals. In a study of obese Shetland ponies, it was necessary to lower feed amounts to 35% of maintenance energy requirement to maintain weight loss equivalent to 1% of ideal body weight per week across a 16-week study period.[38]

Lipotoxicity

Increased adiposity and IR are associated in animals and humans, and several mechanisms have been proposed to explain this finding, including (1) intracellular lipid accumulation, (2) inflammatory mediator production by adipose tissues, and (3) altered adipokine secretion by adipose tissues. The first mechanism is referred to as lipotoxicity and involves repartitioning of fatty acids to skeletal muscle and other tissues, including the liver and pancreas. As adipose tissues reach their capacity for lipid storage, fatty acid uptake by other tissues increases. Randle and colleagues[39] demonstrated in a series of classic studies that a glucose fatty acid cycle exists in which fatty acids compete with glucose for oxidation within muscle. As fatty acid influx increases, intracellular lipid metabolites such as diacylglycerol, fatty acid coenzyme A, and ceramide accumulate, and this increases phosphorylation of serine/threonine sites on insulin receptor substrates 1 and 2, which reduces phosphatidylinositol 3-kinase activity.[40] This disruption in the insulin signaling pathway results in IR.

Inflammation

Adipokines are released from adipocytes and include leptin, resistin, adiponectin, visfatin, apelin, and macrophage chemoattractant proteins.[41] Proinflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukins 1 (IL-1β) and 6 (IL-6) are also released from macrophages residing within adipose tissues. Vick and colleagues[9] provided evidence of systemic inflammation in obese horses by detecting increased expression of TNFα and IL-1β within the blood. However, no differences in proinflammatory cytokine expression were detected in adipose tissues when Burns and colleagues[42] compared insulin-resistant horses with control animals. It is interesting that the same study revealed higher mRNA expression of IL-1β and IL-6 mRNA in nuchal ligament adipose tissue when compared with omental, retroperitoneal, mesocolic, and tail head depots, which supports assertions that the cresty neck is an important phenotypic marker for IR.[6,22] More recently, the same research group reported increased macrophage chemoattractant protein-2 (MCP-2) mRNA expression within omental adipose tissue samples.[43] Omental adipose tissues had greater MCP-2 expression than other adipose tissue depots, and mRNA abundance was significantly higher in insulin-resistant horses.

Omental adipose tissue depots warrant close examination because visceral adiposity is an important component of MetS in humans.[44] Waist circumference is often measured to assess adiposity and abdominal obesity is predictive for IR in humans.[45] Potential explanations for this association include (1) increased release of fatty acids into the portal circulation leading to hepatic IR, (2) higher adipokine and inflammatory cytokine secretion by visceral adipose tissues, and (3) greater expansion of omental adipose tissues compared with subcutaneous tissues in response to overall adipose tissue dysfunction.[44] The first explanation centers on the findings that omental tissues have higher rates of lipolysis and that fatty acids are carried to the liver by the portal circulation. As explained earlier, hepatic IR results

in decreased insulin clearance and therefore hyperinsulinemia, increased glucose production, and very low-density lipoprotein (VLDL) secretion. Higher VLDL-triglyceride concentrations have been detected in obese insulin-resistant horses.[6]

Abdominal obesity might also be connected with IR through altered cortisol production within visceral adipose tissues; specifically, increased 11-β hydroxysteroid dehydrogenase 1 (11βHSD1) activity.[1] Preadipocytes within adipose tissue are converted to adipocytes under the influence of corticosteroids, and these cells produce 11βHSD1, which locally amplifies glucocorticoid action. Diet-induced obesity leads to increased visceral fat preadipocyte differentiation in wild-type but not 11βHSD1 (−/−) mice, and this suggests that 11βHSD1 (ketoreductase) activity is augmented in mouse mesenteric preadipocytes, where it contributes to visceral fat accumulation.[46] In humans, mesenteric and omental adipose tissues are thought to play a more important role in the development of type 2 diabetes mellitus.[47] Only one published study[48] describes the measurement of 11βHSD1 activity in adipose tissues collected from horses, and omental fat was not examined. The results suggested that some horses with EMS had higher 11βHSD1 activity within subcutaneous adipose tissues, but groups did not differ significantly. Further studies are therefore required to examine 11βHSD1 activity within omental adipose tissues collected from insulin-resistant horses.

Adipokines

Two adipokines have been examined to date in horses: leptin and adiponectin. Leptin is sometimes referred to as the satiety factor because this adipokine is released by adipose tissues when energy supplies are plentiful.[49] Receptors on neurons found within the arcuate nucleus of the hypothalamus respond to circulating leptin concentrations, with both appetite-stimulating (orexigenic) and satiety (anorexigenic) neurons expressing leptin receptors. Activation of leptin receptors on orexigenic neurons causes downregulation and suppressed appetite. Leptin signaling also increases pro-opiomelanocortin synthesis and therefore the production of α melanocyte-stimulating hormone, which is an agonist for MC4R. As explained earlier, MC4R is involved in appetite and body weight regulation, and defects in the gene for this receptor are monogenic causes of obesity and body fat distribution in humans.[50]

Higher leptin concentrations are detected in insulin-resistant horses and ponies,[5,6,8,51] and this might represent a state of leptin resistance. Hyperleptinemia has been associated with obesity,[6,8] but horses with leaner BCSs are also affected.[51] Cut-off values for defining hyperleptinemia have differed among studies, depending on whether concentrations are measured as a diagnostic test or are used to define study groups. Carter and colleagues[5] determined a cut-off value of 7.3 ng/mL to predict the occurrence of laminitis in ponies using receiver operating characteristic plots, whereas horses were allocated to normoleptinemic (<5 ng/mL) or hyperleptinemic (>12 ng/mL) groups in another report.[52] In the latter study, hyperleptinemic horses were insulin resistant when compared with horses of the same body condition that had low leptin concentrations. These findings suggest that leptin concentrations can be measured to detect IR in horses and that hyperleptinemia is a component of EMS. Leptin resistance is a concept that warrants consideration, because owners have subjectively observed that horses and ponies with EMS show greater appetite and consume more grass when allowed to graze freely. Leptin resistance might also affect metabolic efficiency, because concentrations of this hormone increase in the late summer as horses accumulate body fat mass and then decline again in the winter.[51] It is therefore conceivable that horses with EMS maintain a state of leptin resistance throughout the year and gain weight as a result.

Adiponectin is considered an insulin-sensitizing adipokine, and blood concentrations are positively correlated with insulin sensitivity in humans and animals.[41,53] This protein is secreted as a homotrimer and circulates as trimers, hexamers, and high molecular weight (HMW) multimers composed of 4 to 6 noncovalently bonded trimers. Kearns and colleagues[8] used a murine/rat enzyme-linked immunosorbent assay (ELISA) to measure total adiponectin, and found that blood concentrations were inversely proportional to body fat mass in horses. A validated assay for total adiponectin is no longer available for horses, but results of a preliminary study using a commercially available ELISA for human HMW adiponectin have recently been reported.[54] Lower concentrations were detected in obese horses and those with evidence of systemic inflammation.

HMW adiponectin is the metabolically active form of adiponectin, but results of studies performed in humans have been mixed with respect to the importance of measuring this isoform. One group reported that HMW adiponectin concentrations are an independent predictor of insulin sensitivity, whereas another concluded that HMW and total adiponectin were equally useful for diagnosing IR.[55,56] Additional studies are required to determine whether HMW concentrations can be used to diagnose IR in horses.

DIAGNOSIS

Screening Tests

Screening testing for EMS is outlined in **Box 1**. EMS should be suspected when an obese horse with regional adiposity presents for examination, particularly if laminitis is also detected. Most owners describe their horses as easy keepers when providing a history, and sometimes report that related horses have suffered from obesity and

Box 1
Screening diagnostic testing for EMS

Screening tests

Historical information

- Owner reports that the horse is an easy keeper (high metabolic efficiency)

Physical examination findings

- Obese (BCS $\geq$7/9)
- Pronounced neck crest (score $\geq$3/5)
- Other evidence of regional adiposity (tail head, prepuce, mammary gland region)
- Divergent growth rings (founder lines) or lameness associated with laminitis

Blood testing (leave only one flake of hay after 10:00 PM; collect blood in the morning)

- Fasting glucose concentration above reference range (>110 mg/dL)
- Fasting insulin concentration >20 μU/mL
- Fasting leptin concentration >7 ng/mL

Data from Henneke DR, Potter GD, Kreider JL, et al. Relationship between condition score, physical measurements and body fat percentage in mares. Equine Vet J 1983;15:371–2; Carter RA, Geor RJ, Burton SW, et al. Apparent adiposity assessed by standardised scoring systems and morphometric measurements in horses and ponies. Vet J 2009;179:204–10; Coat-A-Count insulin radioimmunoassay, Siemens Medical Solutions Diagnostics, Los Angeles, CA; Multispecies leptin radioimmunoassay, Millipore Inc, St Charles, MO.

laminitis. Fasting blood glucose and insulin concentrations should be measured to screen for hyperglycemia and hyperinsulinemia, which serve as indicators of IR. It is also advisable to measure plasma adrenocorticotropin hormone in horses older than 10 years because pituitary pars intermedia dysfunction (PPID) can develop in EMS horses as they age. Leptin measurements are not currently offered by commercial laboratories, but it is expected that testing will be introduced soon. Plasma triglyceride concentrations are currently available and can be requested as part of a plasma biochemistry analysis. Hypertriglyceridemia is more commonly detected in ponies with EMS[4,5] than in horses.[6]

Resting glucose and insulin concentrations are usually measured in a single blood sample to screen for hyperglycemia and hyperinsulinemia, but analysis of multiple samples increases the accuracy of testing. A standardized approach is recommended, which consists of leaving only one flake of hay with the horse after 10:00 PM the night before and then collecting blood the next morning. Blood samples should be kept cool using ice packs or a refrigerator and then sent to an established laboratory.

Blood glucose concentrations are within reference range in most insulin-resistant horses because euglycemia is maintained through increased pancreatic insulin secretion. However, glucose concentrations should always be measured to detect uncompensated IR or diabetes mellitus. Some of these patients can only be identified by detecting hyperglycemia because insulin concentrations have returned to reference range as a result of pancreatic insufficiency.

At present, the most useful screening test for IR is the resting insulin concentration, which must be performed after a short fast to minimize the impact of feeding. As with many tests, the result is more likely to be a true positive the further it falls outside of reference range. A markedly elevated (>100 μU/mL) fasting insulin concentration therefore serves as a good indication of IR. However, it is more difficult to interpret results that are closer to reference range, and breed-specific ranges are needed to improve accuracy. At present, a cut-off value of 20 μU/mL is recommended for the radioimmunoassay (Coat-A-Count insulin radioimmunoassay, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA) commonly used by commercial laboratories, with blood collected under fasting conditions. However, reference ranges for other types of insulin assay should be used where appropriate.

The glucose-to-insulin ratio can also be calculated by dividing the glucose concentration in mg/dL by the insulin concentration in μU/mL (or mU/L). Proponents of this test consider a ratio below 10 to indicate IR and refer to horses with ratios less than 4.5 as severely insulin-resistant or decompensated. This test is not recommended because results are confounded by stress-induced hyperglycemia and glucose consumption by erythrocytes when samples are collected improperly. Furthermore, the ratio does not take into account differences in insulin assays, whereas hyperinsulinemia can be defined by the individual laboratory.

Proxy measurements have also been used to assess insulin sensitivity and pancreatic insulin secretion in horses.[29] The 2 proxies used are the reciprocal of the square root of insulin (RISQI) and the modified insulin to glucose ratio (MIRG). The RISQI represents the degree of insulin sensitivity (a low number indicates IR) and the MIRG represents the ability of the pancreas to secrete insulin. Horses with compensated IR have higher MIRG values. The RISQI value is more important, and can be easily calculated by dividing 1 by the square root of the insulin concentration. A RISQI less than 0.29 indicates IR, which is equivalent to a serum insulin concentration of 12 μU/mL. This method is not recommended, because values were established for a specific group of animals and 20 μU/mL is a more appropriate cut-off value for hyperinsulinemia.

Dynamic Tests

Dynamic tests for EMS are listed in **Box 2**. It is necessary to perform a dynamic test (see **Box 2**) when the animal exhibits physical characteristics of EMS, but screening test results are equivocal. Testing is also recommended to assess the degree of IR and monitor progress. The combined glucose-insulin test (CGIT) was established by Eiler and colleagues[57] and can be performed under field conditions. Euglycemic-hyperinsulinemic clamp and FSIGTT procedures are used in research studies, but the CGIT is a more practical test that requires fewer samples.[58]

When the CGIT is performed, insulin sensitivity is assessed by measuring the time for blood glucose concentrations to return to baseline and the insulin concentration at 45 minutes. Blood glucose concentrations are measured at each time point with a hand-held glucometer until a concentration below baseline is detected, and then this time is recorded for future reference. A blood sample is also collected at 45 minutes and is submitted for the measurement of insulin. An alternative approach is to collect 2 blood samples (0 and 45 minutes) and submit them to a commercial laboratory for glucose and insulin measurements. When this test is used, IR is diagnosed by detecting a blood glucose concentration higher than baseline at 45 minutes[6] or an insulin concentration greater than 100 μU/mL at the same time point. Hypoglycemia is a rare complication of testing, and can be addressed by injecting 50% dextrose (120 mL) intravenously and feeding the horse.

An oral sugar test has recently been developed to assess horses in the field.[59] This oral glucose tolerance test is performed using corn syrup (Karo Light Syrup, Ach Food

Box 2
Dynamic diagnostic testing for EMS

Combined glucose-insulin test

Method

- Perform under fasting conditions (leave one flake of hay after 10:00 PM)
- Obtain a preinfusion blood sample to measure the baseline glucose concentration
- Inject 150 mg/kg body weight 50% dextrose solution intravenously, immediately followed by 0.10 U/kg body weight regular insulin. For a horse weighing 500 kg, inject 150 mL 50% dextrose and 0.50 mL of 100 U/mL insulin
- Collect blood at 1, 5, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135, and 150 minutes
- Measure insulin concentration at 45 minutes

Interpretation

- Insulin resistant if the blood glucose concentration is above baseline or insulin concentration is greater than100 μU/mL at 45 minutes

Oral sugar test

Method

- Fast horse before testing (leave one flake of hay after 10:00 PM)
- Owner administers Karo Light Corn Syrup orally using two 60-mL catheter-tip syringes at a dosage of 15 mL per 100 kg (75 mL for a 500-kg horse)
- Collect one blood sample 60–90 minutes later

Interpretation

- Insulin concentration greater than 60 μU/mL at either time point indicates insulin resistance

Companies Inc, Cordova, TN, USA), which can be purchased and administered by the owner. Corn syrup contains glucose, maltose, maltotriose, and other sugars, and 1 mL syrup provides 1 g total glucose-based digestible carbohydrates. A dose of 150 mg/kg is used, which is equivalent to 0.15 mL/kg or 15 mL per 100 kg body weight (75 mL for a 500-kg horse). Results of a preliminary study indicate that blood insulin concentrations exceed 60 μU/mL at 60, 75, and 90 minutes in insulin-resistant horses. It is therefore recommended that the veterinarian arrive at the farm in time to collect a blood sample 60 to 90 minutes after the test dose has been administered by the owner. Corn syrup can be administered with a dose syringe and is very palatable to horses. This test was developed to address concerns that current screening tests fail to detect horses with more pronounced glucose and insulin responses to feeding.

MANAGEMENT

EMS is a disorder that should be managed with diet, housing, and exercise interventions. The 2 principal strategies for addressing IR in horses are to induce weight loss in obese horses and improve insulin sensitivity through dietary management and exercise.

Weight Reduction

Obese horses should be placed on a weight reduction diet consisting of hay plus protein/vitamin/mineral supplement. Horses should initially receive hay in amounts equivalent to 1.5% of ideal body weight per day (ie, 7.5 kg for a 500-kg horse), and this amount should be lowered to 1% of initial body weight after 1 month if the horse or pony fails to lose weight. Sweet feed should be eliminated from the diet, and horses cannot be allowed to graze on pasture during the weight loss period. In a recent study, restriction of dry matter intake to 1% of initial body mass for 16 weeks was shown to be an effective strategy for inducing weight loss in overweight and obese ponies.[60] The minimum amount of hay recommended for horses is 1% of body weight per day.[61] Increased physical activity promotes weight loss by increasing energy expenditure, so obese horses that are free of laminitis should be exercised as frequently as possible. It is recommended that obese horses be exercised under saddle (or on a lounge line) 4 to 7 days a week for a minimum of 30 minutes at a trot or canter, excluding the time required for warm up and cool down.

Analysis of hay is recommended to ensure that the nonstructural carbohydrate (NSC) content of the forage is low. Equi-analytical Laboratories (Ithaca, NY; www.equi-analytical.com) analyzes hay and provides starch, ethanol-soluble carbohydrate (ESC), and WSC content as percentages of dry matter. ESCs include simple sugars such as monosaccharides and disaccharides, whereas the WSC measurement includes the same sugars plus long-chain fructans. The NSC content of the hay is calculated by taking the sum of WSC and starch values. Some nutritionists consider it more appropriate to exclude long-chain fructans and take the sum of ESC and starch values to calculate NSC, because long-chain fructans are primarily digested in the large intestine and are not expected to elicit postprandial glucose and insulin responses.

A general recommendation is to select hay with NSC content of less than 10% (dry matter basis) for insulin-resistant horses and ponies. However, the importance of NSC content depends on the severity of IR and hyperinsulinemia in the individual animal. Acquiring hay with less than 10% NSC content is very important for horses and ponies with marked fasting hyperinsulinemia (>100 μU/mL), but greater flexibility can be shown when managing mildly affected animals. Most horses with EMS suffer from

obesity, and the reversal of this condition has the greatest influence on insulin sensitivity. Because low-NSC hay usually contains less digestible energy, it can also be selected to promote weight loss.

This review has primarily focused on the obese phenotype because this is the most common manifestation of EMS. However, some affected animals exhibit a leaner body condition, with expanded adipose tissue deposits in specific regions of the body. Examples include (1) previously obese horses that have lost weight after effective management and (2) older animals that have developed PPID, yet remain affected by EMS. In the first situation, IR remains present or will develop again if the patient is allowed to gain weight again. In the case of PPID, anecdotal reports suggest that the layering of this endocrinopathy on top of preexisting EMS exacerbates IR and increases the risk of laminitis. Pergolide treatment is warranted in these cases. Leaner horses that are insulin resistant or have a history of this problem must receive sufficient energy for maintenance without inducing obesity or exacerbating IR; this can be achieved by increasing the amount of hay fed or providing a low-NSC pelleted feed designed for insulin-resistant horses. Each individual horse must be fed according to its body condition and rate of weight gain. Most low-NSC feeds are palatable, but it may take several weeks for the horse to accept a new feed.

Pasture Access

Obesity often develops in horses that are predisposed to EMS when they are given free access to pasture and rarely exercised. Feed intake can be very high when horses are permitted to graze on large pastures or after grass quality increases as a result of reseeding and fertilization. This form of overfeeding is difficult to explain to owners, and represents an important interaction between the metabolism of the individual horse and its diet. Because energy intake cannot be controlled when horses are grazing freely, access to pasture must be limited while inducing weight loss. Strategies for limiting grass consumption on pasture include short (<1 hour) turnout periods twice daily, confinement in a small paddock, round pen, or area enclosed with electric fence, or use of a grazing muzzle. Horses should be housed in dirt paddocks or small grass lots the rest of the time, and addition of a companion to the enclosure increases exercise. Pasture access should also be restricted because affected animals are predisposed to laminitis.[12]

Pasture access should be incrementally increased by 1 hour per turnout per week once obesity and IR have resolved, but body condition should be monitored closely because genetically predisposed animals will return to an obese insulin-resistant state if managed inappropriately. Even when horses have been returned to full pasture access, care should be taken to restrict grazing time when the grass is going through dynamic phases, such as rapid growth in the spring and late summer or at the onset of cold weather in the fall. Horses and ponies with EMS that fail to respond to management or develop laminitis again when permitted to graze must be held off pasture indefinitely.

MEDICAL TREATMENT

Veterinarians have a responsibility to recommend management changes and discourage horse owners from administering drugs as a substitute, but there are 2 indications for pharmacologic intervention: (1) short-term (3–6 months) treatment while management changes are taking effect, and (2) refractory cases.

Levothyroxine Sodium

When administered at high dosages levothyroxine induces weight loss in horses, and this is accompanied by an increase in insulin sensitivity.[62–64] In a recent study, pretreatment with levothyroxine for 14 days also prevented healthy horses from developing IR following endotoxin infusion.[65] Levothyroxine has been administered at an approximate dose of 0.1 mg/kg, which is rounded to 48 mg per day for horses weighing 450 to 525 kg. It is assumed that levothyroxine induces weight loss by raising circulating thyroxine concentrations and stimulating basal metabolic rate. Weight loss can be enhanced during treatment by restricting caloric intake and increasing exercise. Horses should not be permitted to graze on pasture because levothyroxine is likely to induce hyperphagia, which offsets its effects on body weight. Levothyroxine is primarily administered for the purpose of accelerating weight loss in obese horses, and can be prescribed for 3 to 6 months while other management practices are instituted.

Metformin Hydrochloride

Metformin is a biguanide drug that is administered to control hyperglycemia and increase tissue insulin sensitivity in humans with diabetes mellitus. This drug suppresses hepatic glucose production by activating AMP-activated protein kinase, which inhibits gluconeogenesis and lipogenesis while increasing fatty acid oxidation and lipolysis.[66] Two key gluconeogenesis enzymes, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, are inhibited by metformin through this mechanism. The insulin-sensitizing effects of metformin may also be mediated by skeletal muscle adenosine monophosphate kinase (AMPK), causing increased GLUT4 abundance within cell membranes and enhanced glucose uptake.[67] One study also describes AMPK-independent effects of metformin on cardiac muscle, with results indicating that p38 mitogen-activated protein kinase and protein kinase C pathways are activated.[68]

Only a small number of studies have been performed to examine the efficacy of metformin in horses. Durham and colleagues[69] reported that resting insulin concentrations and proxy measures of insulin sensitivity improved in insulin-resistant horses and ponies with metformin treatment (15 mg/kg every 12 hours orally). Administration of metformin at this dosage was associated with positive clinical outcomes, but a subsequent study revealed that the oral bioavailability of this drug is low in a horses.[70] A single dose of 3 g metformin has oral bioavailability of 7.1% $\pm$ 1.5% in fasted horses and 3.9% $\pm$ 1.0% in fed animals.[70] In a recent study, metformin was administered orally to 6 horses with EMS for 14 days after they were moved from stalls to grass paddocks, which was expected to exacerbate IR. All horses received metformin (15 mg/kg every 12 hours) for 2 weeks, followed by a washout period, and then treatment at a higher dosage (30 mg/kg every 12 hours) for 2 additional weeks.[71] Metformin treatment did not affect insulin sensitivity, but resting insulin concentrations decreased in response to treatment at the higher dosage. Of note, insulin sensitivity increased in response to turnout, which supports recommendations to provide horses with adequate space for exercise. At this point in time metformin is still recommended for the management of IR in horses, but further research is required to determine the appropriate dosage for horses.

Other Antidiabetic Drugs

Pioglitazone is the only other insulin-sensitizing drug that has been evaluated to date in horses. Healthy horses were treated with pioglitazone (1 mg/kg every 24 hours orally)

for 14 days and then challenged with lipopolysaccharide.[72] Treatment with pioglitazone did not alter resting insulin sensitivity or prevent endotoxin-induced IR, but insulin receptor mRNA expression increased in skeletal muscle. Pioglitazone belongs to the thiazolidinedione class of antidiabetic drugs that includes rosiglitazone. These drugs stimulate peroxisome proliferator-activated receptor-γ (PPARγ), which is a nuclear receptor that regulates genes involved in glucose and lipid metabolism. Activation of PPARγ increases glucose uptake into adipose, muscle, and liver tissues, stimulates lipogenesis, and inhibits hepatic gluconeogenesis and glycogenolysis. Thiazolidinedione drugs improve glycemic control and increase insulin sensitivity in humans, but further research is required in horses.

SUMMARY

EMS is a clinical syndrome associated with laminitis that includes increased adiposity, hyperinsulinemia, and insulin resistance. This syndrome should be suspected in horses with generalized obesity and/or regional adiposity, and horses can be screened for insulin resistance by measuring resting glucose and insulin concentrations. Hyperinsulinemia is usually detected in insulin-resistant horses, while blood glucose concentrations are maintained within reference range. A simple oral sugar test can also be performed in the field to test for insulin resistance, and the CGIT is used to confirm the problem. Management focuses on diet and exercise interventions to address obesity, and most horses respond well to this approach. Horses that remain insulin resistant after weight loss and those with a leaner body condition are more challenging to diagnose and manage. Medical treatments are sometimes necessary in these cases, and more studies are required to assess insulin-sensitizing drugs in horses.

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