ACVIM Consensus Statement
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Equine Metabolic Syndrome

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The term equine metabolic syndrome (EMS) was first introduced to veterinary medicine in 2002 when Johnson[1] proposed that obesity, insulin resistance (IR), and laminitis were components of a clinical syndrome recognized in horses and ponies. The study of EMS is therefore in its infancy, so the following consensus statement reflects our current knowledge of this condition. We anticipate that defining features of the EMS phenotype, approaches to diagnostic testing, and management options will be expanded and updated as further research is performed.

"EMS" was adopted as the name for this condition because of similarities with the metabolic syndrome (MetS) in humans, which is a collection of risk factors assessed to predict the occurrence of coronary artery disease and type 2 diabetes mellitus in people.[2] Despite alternative nomenclature having been proposed previously (eg, peripheral Cushing's syndrome, prelaminitic metabolic syndrome), it was the unanimous decision of the consensus panel to support the use of the term EMS because it has gained wide acceptance and is appropriate when used to define a clinical syndrome unique to equids. The panel proposed that the EMS phenotype for the majority of affected equids should include:

- Increased adiposity in specific locations (regional adiposity) or generally (obesity). Regional adiposity is characterized by expansion of subcutaneous adipose tissues surrounding the nuchal ligament in the neck (cresty neck), development of fat pads close to the tail head, or fat accumulation behind the shoulder or in the prepuce or mammary gland region. Obesity is observed in the majority of cases, but some affected equids have a leaner overall body condition and regional adiposity, and others are normal in appearance. These different phenotype variations require further study.
- IR characterized by hyperinsulinemia or abnormal glycemic and insulinemic responses to oral or IV glucose and/or insulin challenges.
- A predisposition toward laminitis. Clinical or subclinical laminitis that has developed in the absence of recognized causes such as grain overload, colic, colitis, or retained placenta.

Additional components of the EMS phenotype that warrant further consideration include:

- Hypertriglyceridemia or dyslipidemia as a component of EMS in some cases.[3–5] Increased very low-density lipoprotein triglyceride concentrations have also been detected in horses with EMS.[5]
- Hyperleptinemia resulting from increased secretion of the hormone leptin by adipocytes in response to IR or a state of leptin resistance.[6] Leptin is referred to as a satiety factor because it signals the hypothalamus that a state of energy excess exists within adipose tissues.[7]
- Arterial hypertension[4,8] detected in the summer in laminitis-prone ponies,[8] which is recognized as a key component of MetS related to IR in humans.[9]
- Altered reproductive cycling in mares. Loss of the seasonal anovulatory period[10] and prolongation of the interovulatory period[11] have been described in obese insulin-resistant mares.
- Increased systemic markers of inflammation in association with obesity.[12]

History

Contributing factors for obesity should be assessed from the history, including the quantity of feed provided,

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size and quality of the pasture, and amount of exercise. Horse owners sometimes refer to affected horses and ponies as "easy keepers" or "good doers" because they require a lower plane of nutrition to maintain body weight than other horses.

Previous episodes of laminitis may be described in the history. Mild episodes of bilateral laminitis may have been mistakenly attributed to sole bruising, arthritis, or foot soreness after trimming or shoeing. If laminitis episodes have been recognized in the past, it should be noted whether the onset of lameness was associated with changes in the abundance or composition of pasture grass, or alterations in grain feeding.

Familial patterns have been recognized for EMS,[3] so relevant information about the horse's dam and sire should be collected for future reference.

Clinical Signs

Clinical signs of EMS include regional adiposity, obesity, bilateral lameness attributable to laminitis, and/or evidence of previous laminitis such as divergent growth rings on the hooves. A cresty neck score[13] has been developed to assess the expansion of adipose tissues within the neck region and scores range from 0 to 5. Scores ≥ 3 are often detected in horses or ponies with EMS. 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 at the midpoint of the neck with a tape measure. This measurement is taken halfway between the poll and the withers when the neck is in a normal elevated position.[5] The neck circumference-to-height at withers ratio was recently used to predict the development of pasture-associated laminitis in ponies and a cut-off value of >0.71 was established. Body weight should be measured with a scale or weight tape and body condition scoring[14] can be used to assess generalized obesity.

Pathophysiology

EMS is a complex disorder for which there are more questions than answers at present. The principal components of EMS are increased adiposity, IR, and laminitis, but this syndrome likely encompasses a much wider spectrum of problems that affect energy metabolism, perturb adipocyte function, promote thrombosis, induce inflammation and oxidant stress, and alter vascular endothelial cell function in affected horses.

Adiposity

Environmental (eg, diet, level of physical activity, season) and intrinsic (eg, genetics) factors will affect body fat mass. The mechanisms underlying generalized obesity or regional adiposity in EMS are unknown but chronic overfeeding in association with limited physical activity appears to be a contributing factor. Additionally, horses and ponies with EMS appear to have enhanced metabolic efficiency with respect to the utilization of dietary energy. In this context, it has been suggested that horses and ponies evolutionarily adapted to survival in nutritionally sparse environments are especially predisposed to obesity and IR under modern management conditions in which plentiful feed is available year round. For example, feral and native pony breeds retain strong seasonality with respect to appetite and body condition. Under "feral" conditions these ponies gain weight during the summer months when food is abundant before losing it again during the winter.[a] Seasonal changes in insulin sensitivity also may occur, reflecting alterations in food availability, physical activity, and body condition. Season affected resting serum insulin concentrations in 1 study of obese mares, with higher concentrations detected in December, compared with September, October, and November.[11] In the context of domesticated equids experiencing a chronic state of overnutrition, these seasonal changes in body condition and insulin sensitivity may be replaced by progressive obesity and IR with associated adverse health consequences. More research is required to identify the genetic determinants of metabolic efficiency in horses and the effects of environmental factors such as overnutrition on the expression of these genes.

Adipose tissue is no longer regarded as just an energy storage organ, but an endocrine organ producing many hormones (adipokines or adipocytokines).[15] Adipose tissue dysfunction (with or without obesity) is an important pathophysiologic feature of MetS in humans that may result in IR, systemic inflammation, hypertension, and a prothrombotic status. Adipokines are released from adipocytes and other cells within fat tissues. They include leptin, resistin, adiponectin, visfatin, and apelin as well as inflammatory cytokines released from macrophages and adipocytes such as tumor necrosis factor alpha (TNFα), interleukins 1 (IL-1) and 6 (IL-6), and macrophage chemoattractant protein 1. The inflammatory adipokines may then lead to a self-perpetuating cycle of enhanced adipose tissue inflammation, adipokine synthesis, and secondary acute phase protein synthesis by the liver. Thus obesity in people is characterized by a state of chronic low-grade inflammation.[15]

Few data are available on the pathophysiological effects of obesity or regional adiposity in EMS. Obesity has been associated with reduced insulin sensitivity in horses and ponies,[3,5,10,11,16] although some obese horses have normal insulin sensitivity. Whether obesity induces IR or the insulin-resistant horse is more predisposed to obesity has not been determined. Further contributory factors to obesity and IR may include altered cortisol metabolism within tissues[1] or leptin resistance, a situation in which tissues fail to respond to leptin.[7]

In humans, mesenteric and omental adipose tissues are thought to play a more important role in the development of type 2 diabetes mellitus than adipose tissues elsewhere because fatty acids and adipokines released from these visceral sites enter the portal circulation and have a more profound effect on hepatic metabolism and insulin clearance.[17] This situation is currently being examined in horses to determine whether adipose tissue from the neck crest or abdomen differs from tissues

collected from other locations, but results have not yet been published.

IR

IR involves defects of insulin signaling such as reduced insulin receptor tyrosine kinase activity and reduced postreceptor phosphorylation steps that impinge on metabolic and vascular effects of insulin.[18] There are two primary theories linking obesity to IR: (1) the down-regulation of insulin signaling pathways induced by adipokines and cytokines produced in adipose tissue; and (2) the accumulation of intracellular lipids in insulin-sensitive tissue such as skeletal muscle (lipotoxicity).[19] The natural equine diet contains little fat, but excess glucose can be converted into fat via de novo lipogenesis. Fats are used for energy or stored as triglyceride within cells. When the storage capacity of adipose tissues is exceeded, fats are directed toward nonadipose tissues (repartitioning). Skeletal muscle, liver, and pancreatic tissues attempt to utilize fats by increasing β-oxidation, but lipid can accumulate within these tissues and alter normal cellular functions, including insulin signaling.

Laminitis

We are limited at present to the knowledge that IR and/or hyperinsulinemia predispose ponies to pasture-associated laminitis and that the condition can be experimentally induced by infusing supraphysiological amounts of insulin IV over 2–3 days.[3,20] Potential mechanisms relating obesity, hyperinsulinemia, and IR to laminitis are largely extrapolated from studies in other species and include endothelial cell dysfunction within blood vessels of the foot,[21] digital vasoconstriction,[22] impaired glucose uptake by epidermal laminar cells,[23] altered epidermal cell function or mitosis,[24]and matrix metalloproteinase activation by glucose deprivation or reactive oxygen species.[23]

Insulin has vasoregulatory actions and it was the consensus of the panel that this represents a plausible link between IR and laminitis in horses. Vasodilation normally occurs in response to insulin through the increased synthesis of nitric oxide (NO) by endothelial cells.[25,26] However, insulin may also promote vasoconstriction by stimulating the synthesis of endothelin-1 (ET-1)[26] and activating the sympathetic nervous system.[27] Activation of the insulin receptor stimulates at least two different signaling pathways within the vascular endothelial cell.[28] NO is secreted when the phosphatidylinositol 3-kinase (PI3K) pathway is activated, whereas activation of the mitogen-activated protein kinase (MAPK) pathway leads to the release of ET-1. IR states in humans have been found to involve selective pathway inhibition such that the NO synthetic PI3K pathway is inhibited whereas the MAPK pathway is unaffected and may be overstimulated because of compensatory hyperinsulinemia, which results in increased ET-1 synthesis.[25,29] Vasoconstriction may therefore be promoted in the insulin-resistant animal as NO production decreases, which might impair the ability of vessels to respond to vascular challenges.

Epidemiology

To the panel's knowledge, there are no published studies on the epidemiology of EMS although there are a few reports on the prevalence of obesity and hyperinsulinemia in populations of ponies and horses.[30,b,c,d] Anecdotally, Welsh, Dartmoor, and Shetland ponies and Morgan Horse, Paso Fino, Arabian, Saddlebred, Spanish Mustang, and warmblood breeds appear to be more susceptible to EMS. However, the panel emphasized that EMS can be prevented through good management practices, so breed susceptibility should be viewed accordingly. EMS also occurs in other light horse breeds, including Quarter Horses and Tennessee Walking Horses, but is rarer in Thoroughbreds and Standardbreds. Miniature horses, donkeys, and draft horses require further study to determine the prevalence of EMS in these groups.

Susceptibility to EMS may be established from before birth, and obesity develops in some horses as soon as they reach maturity. However, most horses with EMS are between 5 and 15 years of age when veterinary or farrier services are first requested because of laminitis.

A seasonal pattern has been identified for laminitis in the United States, with the highest incidence of pasture laminitis around May and June (late spring/early summer).[3,31] This seasonal rise in laminitis incidence has been attributed to increased nonstructural carbohydrate (NSC) consumption from pasture forage. In the United Kingdom, the highest incidence of pasture laminitis was during the summer (June and July), when sunshine hours and presumably forage NSC content were greatest.[e] This observation provides further circumstantial evidence to suggest a link between grass carbohydrate content and laminitis incidence. Serum insulin concentrations and the reciprocal inverse square of insulin proxy estimate of insulin sensitivity measured in ponies predisposed to laminitis suggested a decrease in insulin sensitivity during summer, and this was attributed to changes in pasture carbohydrate composition.[8] Results suggested that aspects of the EMS phenotype in ponies may be latent under conditions of lower or restricted dietary water-soluble carbohydrate (WSC) content, but become apparent when carbohydrate intake increases. Pasture carbohydrate content and climate/seasonal effects are inextricably linked. During periods of high sunshine, when sugars are produced in excess of the energy requirement of the pasture for growth and development, they are converted into storage, or reserve, carbohydrates, such as fructans and starches.[32]

Diagnosis

EMS can be diagnosed by obtaining a complete history, performing a physical examination, taking radiographs of the feet, and conducting laboratory tests. Physical examination should include assessment of the horse for evidence of regional adiposity, including adipose tissue expansion within the neck crest, and body condition scoring. Current screening tests for IR focus upon the measurement of glucose and insulin concentra-

tions in single blood samples, although dynamic tests are necessary to properly assess insulin sensitivity. An important goal for the future is the development of a panel of tests to diagnose EMS.

Hyperglycemia is rarely detected in horses with EMS because most animals maintain an effective compensatory insulin secretory response in the face of IR. However, blood glucose concentrations are often toward the higher end of reference range indicating partial loss of glycemic control. If persistent hyperglycemia is detected, a diagnosis of diabetes mellitus should be considered. Type 2 diabetes mellitus occurs in horses and may be more common than thought previously.[33] This diagnosis should be considered when hyperglycemia cannot be attributed to other causes such as stress, recent feeding, administration of α-2 agonist drugs, or inflammatory processes.

Hyperinsulinemia in the absence of confounding factors such as stress, pain, and a recent feed provides evidence of IR in horses and ponies. However, resting insulin concentrations are not found to be increased in all cases, so dynamic testing provides the most accurate diagnosis of IR. It should also be recognized that reference ranges vary among laboratories, in part because of differences in the assay used. More research is required to determine cut-off values for hyperinsulinemia, but a value of 20 μU/mL[f] is suggested as a general guideline for the upper limit of serum/plasma insulin concentrations in normal horses and ponies.

Sampling conditions are important when diagnosing the chronic IR associated with EMS. Cortisol and epinephrine released as a result of pain or stress lower tissue insulin sensitivity and raise resting glucose and insulin concentrations.[34,35] Insulin concentrations are likely to be higher in a horse that is currently suffering from laminitis, so testing should be delayed until after the pain and stress of this condition has subsided. Blood samples should be collected after an approximately 6-hour period of feed withholding, ideally between 8:00 and 10:00 AM. These conditions can be achieved by providing not more than 1 flake of low-NSC grass hay per 500 kg bodyweight no later than 10:00 PM the night before sampling. Under these conditions, hyperinsulinemia (>20 μU/mL) provides evidence of IR. If hyperinsulinemia is not detected, but other components of the EMS phenotype are recognized, a dynamic test of insulin sensitivity should be performed.

Dynamic testing for evaluation of insulin sensitivity is recommended because tissue insensitivity to insulin may only be revealed when glycemic control is challenged by inducing hyperglycemia. A number of tests can be used for this purpose, and an ideal test for diagnosing IR in horses has not been established to date.[36] Testing should be conducted under the same conditions as blood sampling for resting glucose and insulin measurements. Horses must be tested after the pain and stress of laminitis has subsided, and after an approximately 6-hour fast to limit confounding effects of recent feed consumption. Oral or IV glucose tolerance tests can be performed to raise blood glucose and insulin concentrations and determine the height and width of the resulting curve. Area under the curve values provide the best measure of glucose tolerance, although the peak concentration and time taken for concentrations to return to baseline can also be evaluated. The combined glucose-insulin test (CGIT) developed by Eiler et al[37] can also be used to diagnose IR in horses.[5] Insulin is injected immediately after dextrose to lower blood glucose concentrations. Advantages of the CGIT include the shorter time required for testing and information gained about both the glycemic and insulinemic responses. A CGIT is performed by first obtaining a preinjection blood sample for baseline glucose and insulin measurements, and then injecting 150 mg/kg body weight (bwt) 50% dextrose solution IV, immediately followed by 0.10 U/kg bwt regular insulin IV.[37] These dosages are equivalent to 150 mL of 500 mg/mL (50%) dextrose and 0.50 mL of 100 U/mL insulin for a horse weighing 500 kg. Insulin should be drawn into a tuberculin syringe and then transferred into a larger syringe containing 1.5-mL sterile saline (0.9% NaCl) before injection. Blood glucose concentrations are measured at 1, 5, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135, and 150 minutes postinfusion.

When the CGIT is performed in healthy animals, blood glucose concentrations return to below the baseline value by 45 minutes, so preliminary results are available within 1 hour if a glucometer is used. Blood collected at 0 and 45 minutes is submitted for insulin assay and this allows the insulin response to be evaluated. Horses with insulin concentrations >100 μU/mL at 45 minutes are secreting more insulin than normal and/or clearing the hormone from the circulation at a slower rate. This is interpreted as an indication of IR. The test can be abbreviated to 60 minutes when used in the field, but it is advisable to complete all of the measurements so that the horse's complete response can be recorded for future comparison. Hypoglycemia is a potential complication of testing, although this is rarely encountered in the patients selected for testing. If clinical signs of hypoglycemia (sweating, weakness, and muscle fasciculation) are recognized or if blood glucose concentrations fall below 40 mg/dL (2.2 mmol/L), administer 60 mL of 50% dextrose IV and repeat as necessary.

In addition to glucose, it has been found that feeding some other carbohydrates to ponies induces an exaggerated insulin response in IR individuals. These carbohydrates include inulin, a type of fructan carbohydrate.[38] Furthermore, the administration of dexamethasone also elicits this exaggerated insulin response.[5] These observations may have implications for the likely causes of hyperinsulinemia in horses or ponies with EMS that are grazing on pasture, putting them at risk of laminitis. These tests require further validation.

Future directions for diagnostic testing include the development of a test panel consisting of assays that can be performed on a single blood sample. Such a panel might further include the adipokines leptin, adiponectin, and resistin, lipids such as triglyceride and nonesterified fatty acids, fructosamine as a reflection of blood glucose concentrations,[39] and measures of systemic inflammation including TNFα, IL-1, IL-6, C-reactive protein, serum amyloid A, and plasminogen activator inhibitor-1. Red

blood cell count, PCV, iron concentration, and plasma gamma glutamyl transferase (GGT) activity might also be included on the panel. Anemia is sometimes detected in EMS horses, and some affected horses have shown elevated GGT activity that has corresponded with hepatic lipidosis, detected in biopsy and necropsy specimens. Pancreatic insulin secretion may be assessed by measuring serum connecting peptide (C-peptide) concentrations. This peptide is released in equimolar amounts with insulin, but is not cleared from the blood by the liver.[40] Approximately 60% of the insulin secreted by the pancreas is extracted from the portal blood by the liver in healthy humans, so hyperinsulinemia can develop as a result of reduced insulin clearance and/or increased pancreatic secretion. Serum C-peptide concentrations can indicate the relative contributions of these processes. Recent research suggests that reduced insulin clearance significantly contributes to hyperinsulinemia in horses with EMS,[41] so the C-peptide-to-insulin ratio may be useful to further characterize the hyperinsulinemia detected in equids.

Differentiating EMS from Pituitary Pars Intermedia Dysfunction (PPID; Equine Cushing's Disease)

Regional adiposity and laminitis are clinical signs of PPID as well as EMS,[42] so both endocrine disorders should be considered when these problems are detected. EMS may be differentiated from PPID by:

- Age of onset: The EMS phenotype is generally first recognized in younger horses, whereas PPID is more common in older horses; although these disorders may coexist.
- Further clinical signs suggestive of PPID, but not EMS, including delayed or failed shedding of the winter haircoat, hirsutism, excessive sweating, polyuria/polydipsia, and skeletal muscle atrophy.[42]
- Positive diagnostic test results for PPID: For example, detection of an increased plasma adrenocorticotropin hormone concentration in the absence of confounding factors such as pain and stress, and outside of the late summer/autumn period when false positive results occur in healthy horses and ponies.[g]

Reduced glucose tolerance indicative of IR has also been detected in horses with PPID.[43] However, it was the consensus of the panel that normal insulin sensitivity is more common in horses with PPID, which suggests that the relationship between these conditions is complex. Discussion of this subject generated several questions that require further research, including:

1. Does IR only accompany PPID when the animal was insulin resistant before pituitary dysfunction developed? If this is the case, PPID may exacerbate IR, but not be the cause of the problem.
2. If PPID causes IR in some horses, but not others, is this a particular manifestation of the disorder? Are specific hormones responsible for IR in these PPID patients?
3. Are the effects of PPID on insulin sensitivity dependent upon the stage of the condition?
4. Does EMS represent a risk factor for PPID?

The consensus panel recognized that some equids with EMS subsequently develop PPID, so both conditions can occur concurrently. Anecdotal reports suggest that horses and ponies with EMS are predisposed to PPID and pituitary dysfunction develops at a younger age in affected animals. Further research is required in this area, but the panel recommends that equids with EMS be closely monitored for clinical signs of PPID and undergo regular testing for the condition. If PPID is causing and/or exacerbating IR, treatment should improve insulin sensitivity. Pergolide is recommended for the treatment of PPID in equids.[42]

Dietary Management

Dietary management of EMS involves reducing the amount of energy provided in the diet to induce weight loss if the horse or pony is obese and lowering the NSC content of the diet to reduce glycemic and insulinemic responses to meals. Reducing the digestible energy (DE) content of the diet is an important factor in moderating obesity as a contributory factor to EMS. Limiting or eliminating pasture grass from the diet is a key component of this approach because pasture grazing provides DE that cannot be quantified. Obese horses and ponies should be provided a forage diet with mineral/vitamin supplementation. Hay with low NSC content should be selected, which can be determined by submitting a sample for analysis or by purchasing forage with a declared nutrient analysis. Simple sugars, starches, and fructans are NSC, whereas cellulose and hemicelluloses are structural carbohydrates.[32] It was thought previously that fructans undergo minimal hydrolysis until they reach the large intestine of the horse, so they would be less likely to contribute to the glycemic response after a meal. However, there is some evidence indicating that there may be appreciable microbial and acid hydrolysis of fructans before they reach the equine large intestine.[32] Furthermore, insulin-resistant ponies exhibit an insulin response to dietary fructans.[38] It is therefore recommended that NSC be calculated by adding starch and WSC percentages together, and this value should ideally fall below 10% of dry matter when feeding horses or ponies with EMS. Hay can be soaked in cold water for 60 minutes to lower the WSC content if the amount of NSC exceeds 10%.[44] However, a recent study demonstrated that results vary markedly among different hay samples,[45] so this strategy cannot be relied upon to completely address the problem of high WSC concentrations in the hay that is being fed to a horse or pony with EMS.

Weight loss should be induced in obese horses by restricting the total number of calories consumed and by increasing the individual's level of physical activity. In horses that are being overfed, removal of all concentrates

from the diet is sometimes sufficient to induce weight loss. An obese horse should be placed on a diet consisting of hay fed in an amount equivalent to 1.5% of ideal body weight (1.5 lb hay per 100 lb bwt). Hay should be weighed on scales to ensure that correct amounts are fed. If an obese horse or pony fails to lose weight after hay has been fed at an amount equivalent to 1.5% of ideal body weight for 30 days, this amount should be lowered to 1%. However, amounts should not fall below this minimum of 1% and it should be noted that severe calorie restriction may lead to worsening of IR, hyperlipemia, and unacceptable stereotypical behaviors.

Pasture access should be eliminated until insulin sensitivity has improved because carbohydrates consumed on pasture can trigger gastrointestinal events that lead to laminitis in susceptible horses.[46] Mildly affected horses can return to pasture once obesity and IR have been addressed, but care must be taken to restrict pasture access when the grass is going through dynamic phases, such as rapid growth in the spring or preparation for cold weather in the fall. Measurement of pasture grass NSC content at different times of the day has revealed that grazing in the early morning is likely to be safer for horses with IR, except after a hard frost when grasses accumulate WSC.[47] Other risk factors for high fructan content include regular cutting, cool, and bright conditions and predominance of certain grass species such as ryegrass.[32,48] Strategies for limiting grass consumption include short (<1 hour) turnout periods (or hand-grazing), confinement in a small paddock, round pen, or area enclosed with electric fence, or use of a grazing muzzle. Horses and ponies with EMS can have rapid rates of grass intake, so >1–2 hours grazing may be excessive for these animals.[32] Unfortunately, severely insulin-resistant horses that suffer from recurrent laminitis must be kept off pasture permanently. These patients should be housed in dirt paddocks so that they are able to exercise once hoof structures have stabilized. Forage only diets will not provide adequate protein, minerals, or vitamins. Supplementing the forage diet with a low-calorie commercial ration balancer product that contains sources of high-quality protein and a mixture of vitamins and minerals to balance the low vitamin E, vitamin A, copper, zinc, selenium, and other minerals typically found in mature grass hays is therefore recommended. These products are designed to be fed in small quantities (eg, 0.5–1.0 kg total per day).

Insulin-resistant horses with a thinner overall body condition are challenging to manage from a dietary standpoint because hay alone may not meet energy requirements. Commercial low-NSC feeds are available for use in these situations in which digestible fibers (beet pulp or soya hulls) and/or vegetable oils are included in place of starch-rich ingredients. The energy density (ie, DE per kg) of these feeds is variable depending on composition, so energy requirements and the severity of IR must be taken into account before feed selection. It is also better to divide the daily ration into multiple small meals and to feed hay beforehand as this may slow the rate of feed intake and gastric emptying and minimize postfeeding increases in the circulating concentrations of both glucose and insulin. Alternatively, the energy density of the ration can be increased by feeding soaked beet pulp shreds (nonmolassed) or vegetable oil. The latter can be mixed with beet pulp or with hay cubes that have been soaked in water. Corn and soy oils are commonly used in equine rations; 1 standard cup ($\sim$225 mL or 210 g) of vegetable oil provides 1.7 Mcal (7.1 MJ) of DE. Depending on energy requirements, 1/2 to 1 cup of oil can be fed once or twice daily. Smaller amounts (eg, 1/4 cup once daily) should initially be fed, with a gradual increase over a 7- to 10-day period. With all of these strategies, the goal is to lower the glycemic and insulinemic response to the meal, which is the degree to which blood glucose and insulin concentrations rise in response to the feed. Further information regarding the dietary management of obesity and IR in equids is provided in a recent review.[49]

Physical Activity

Regular physical exercise is an effective therapeutic intervention to improve insulin sensitivity in obese insulin-resistant people. An exercise prescription of approximately 200 minutes per week of moderate intensity exercise results in a sustained increase in insulin sensitivity[50,51] and improvements in other risk factors (eg, lipid profile) that are criteria for MetS.[52] Furthermore, improvements in insulin sensitivity associated with physical activity can occur in the absence of weight loss or change in fat distribution.[53] Therefore, subject to the status of foot pain and structural damage, an increase in physical activity is recommended for equids with EMS in order to promote weight loss and improve insulin sensitivity.[54,55] More research is required to determine an optimal exercise prescription for management of EMS, but a general recommendation is to start with 2–3 exercise sessions per week (riding and/or longeing), 20–30 minutes per session. Subsequently, there should be a gradual increase in the intensity and duration of exercise, for example, building to 5 sessions per week.

Medical Management

Most horses and ponies with EMS can be effectively managed by controlling the horse's diet, instituting an exercise program, and limiting or eliminating access to pasture. Many studies have revealed that IR in human subjects is controlled most effectively by changes in lifestyle and diet although these strategies may fail due to lack of self-discipline.[56] Similarly, compliance of the owner/manager is critical to the success of management changes designed to alleviate risk factors for laminitis in EMS.

Pharmaceutical products used to treat IR and type 2 diabetes mellitus in humans primarily include insulin sensitizers comprising metformin (a biguanide) and thiazolidinediones (pioglitazone and rosiglitazone); and insulin secretagogues comprising sulphonylureas (glyburide [glibenclamide], glipizide and glimepiride), repaglinide (a benzoic acid derivative), and nateglinide (a phenylalanine derivative).[57] In horses, only levothyroxine sodium and metformin have thus far received any attention in the context of medical management of IR and EMS.

Levothyroxine Sodium

Weight loss can be induced and insulin sensitivity improved by administering levothyroxine sodium to horses.[58–60] Levothyroxine sodium is given to horses and larger (>350 kg) ponies at a dosage of 48 mg/day in the feed for 3–6 months at the same time that diet and exercise interventions are initiated. Smaller ponies and Miniature horses are given 24 mg levothyroxine sodium per day for the same time period. Treated horses should be weaned off levothyroxine sodium once ideal body weight has been attained by reducing the dosage to 24 mg/day for 2 weeks and then 12 mg/day for 2 weeks.

Serum tT4 concentrations often range between 40 and 100 ng/mL in treated horses, indicating that levothyroxine sodium is being given at a supraphysiological dosage. However, clinical signs of hyperthyroidism such as emaciation, sweating, tachycardia, or tachypnea have not been observed in treated horses.[58,61,62] Benefits of treating horses with levothyroxine at lower dosages for longer periods have not been evaluated scientifically.

Metformin

Positive responses to metformin have been reported in hyperinsulinemic horses and ponies at a dosage of 15 mg/kg twice daily PO.[63] Insulin sensitivity estimated by proxy measures improved in treated animals, without the adverse effect of hypoglycemia. Metformin is a biguanide drug that enhances the action of insulin within tissues at the postreceptor level most likely by promoting AMP-dependent protein kinase.[64] Inhibition of gluconeogenesis and glycogenolysis within the liver appears to be its main mode of action along with many other insulin- and noninsulin-related effects.[65] Results of this first study look promising, but safety studies have not been performed to date in horses, so this must be considered before the drug is prescribed long term. Results of recent pharmacokinetic studies indicate that oral bioavailability of metformin is lower in horses than humans.[66,67] Efficacy might therefore be improved by further investigation of appropriate dosing schedules.

Supplements and Nutraceuticals

Chromium, magnesium, cinnamon, and chasteberry (*Vitex agnus-castus*) are commonly recommended for the management of EMS. It was the consensus of the panel that there is insufficient scientific evidence to support the use of these supplements at this time and that results of controlled studies should be examined before these products are recommended.

Footnotes

[a] Dugdale AHA, Curtis GC, Knottenbelt DC, et al. Changes in body condition and fat deposition in ponies offered an ad libitum chaff-based diet. 12th Congress on the European Society for Veterinary Clinical Nutrition, Vienna, Austria. 2008;39 (abstract)

[b] McGowan CM, Geor R, McGowan TW. Prevalence and risk factors for hyperinsulinemia in ponies. J Vet Intern Med 2008; 22:734 (abstract)

[c] Muno J, Gallatin L, Geor RJ, et al. Prevalence and risk factors for hyperinsulinemia in clinically normal horses in central Ohio. J Vet Intern Med 2009;23:721 (abstract)

[d] Thatcher C, Pleasant R, Geor R, et al. Prevalence of obesity in mature horses: an equine body condition study. The American Academy of Veterinary Nutrition 7th Annual Clinical Nutrition and Research Symposium, Seattle, WA. 2007;6 (abstract)

[e] Katz L, DeBrauwere N, Elliott J, et al. A retrospective epidemiological study of laminitis in one region of the UK. Proceedings of the 40th British Equine Veterinary Association Congress, Harrogate, UK. 2001;199 (abstract)

[f] Measured by Coat-A-Count insulin radioimmunoassay (Siemens Medical Solutions Diagnostics, Los Angeles, CA), Immulite insulin solid-phase chemiluminescent assay (Siemens Medical Solutions Diagnostics), or DSL-1600 insulin radioimmunoassay (Diagnostic Systems Laboratory Inc, Webster, TX)

[g] Donaldson MT, McDonnell SM, Schanbacher BJ, et al. Variation in plasma ACTH concentration and dexamethasone suppression test results in association with season, age, and sex in healthy ponies and horses. J Vet Intern Med 2004;18:414 (abstract)

References

1. Johnson PJ. The equine metabolic syndrome peripheral Cushing's syndrome. Vet Clin North Am Equine Pract 2002;18:271–293.

2. Fulop T, Tessier D, Carpentier A. The metabolic syndrome. Pathol Biol (Paris) 2006;54:375–386.

3. Treiber KH, Kronfeld DS, Hess TM, et al. Evaluation of genetic and metabolic predispositions and nutritional risk factors for pasture-associated laminitis in ponies. J Am Vet Med Assoc 2006;228:1538–1545.

4. Carter RA, Treiber KH, Geor RJ, et al. Prediction of incipient pasture-associated laminitis from hyperinsulinaemia, hyperleptinaemia and generalised and localised obesity in a cohort of ponies. Equine Vet J 2009;41:171–178.

5. Frank N, Elliott SB, Brandt LE, et al. Physical characteristics, blood hormone concentrations, and plasma lipid concentrations in obese horses with insulin resistance. J Am Vet Med Assoc 2006;228:1383–1390.

6. Cartmill JA, Thompson DL Jr., Storer WA, et al. Endocrine responses in mares and geldings with high body condition scores grouped by high vs. low resting leptin concentrations. J Anim Sci 2003;81:2311–2321.

7. Houseknecht KL, Spurlock ME. Leptin regulation of lipid homeostasis: Dietary and metabolic implications. Nutr Res Rev 2003;16:83–96.

8. Bailey SR, Habershon-Butcher JL, Ransom KJ, et al. Hypertension and insulin resistance in a mixed-breed population of ponies predisposed to laminitis. Am J Vet Res 2008;69:122–129.

9. Lamounier-Zepter V, Ehrhart-Bornstein M, Bornstein SR. Insulin resistance in hypertension and cardiovascular disease. Best Pract Res Clin Endocrinol Metab 2006;20:355–367.

10. Gentry LR, Thompson DL Jr., Gentry GT Jr., et al. The relationship between body condition, leptin, and reproductive and hormonal characteristics of mares during the seasonal anovulatory period. J Anim Sci 2002;80:2695–2703.

11. Vick MM, Sessions DR, Murphy BA, et al. Obesity is associated with altered metabolic and reproductive activity in the mare: Effects of metformin on insulin sensitivity and reproductive cyclicity. Reprod Fertil Dev 2006;18:609–617.

12. Vick MM, Adams AA, Murphy BA, et al. Relationships among inflammatory cytokines, obesity, and insulin sensitivity in the horse. J Anim Sci 2007;85:1144–1155.

13. Carter RA, Geor RJ, Burton Staniar W, et al. Apparent adiposity assessed by standardised scoring systems and morphometric measurements in horses and ponies. Vet J 2009;179:204–210.

14. Henneke DR, Potter GD, Kreider JL, et al. Relationship between condition score, physical measurements and body fat percentage in mares. Equine Vet J 1983;15:371–372.

15. Rasouli N, Kern PA. Adipocytokines and the metabolic complications of obesity. J Clin Endocrinol Metab 2008;93:S64–S73.

16. Van Weyenberg S, Hesta M, Buyse J, et al. The effect of weight loss by energy restriction on metabolic profile and glucose tolerance in ponies. J Anim Physiol Anim Nutr (Berlin) 2008;92:538–545.

17. Santosa S, Jensen MD. Why are we shaped differently, and why does it matter? Am J Physiol Endocrinol Metab 2008;295:E531–E535.

18. Kashyap SR, Defronzo RA. The insulin resistance syndrome: Physiological considerations. Diab Vasc Dis Res 2007;4:13–19.

19. Summers SA. Ceramides in insulin resistance and lipotoxicity. Prog Lipid Res 2006;45:42–72.

20. Asplin KE, Sillence MN, Pollitt CC, et al. Induction of laminitis by prolonged hyperinsulinaemia in clinically normal ponies. Vet J 2007;174:530–535.

21. Jansson PA. Endothelial dysfunction in insulin resistance and type 2 diabetes. J Intern Med 2007;262:173–183.

22. Sarafidis PA, Bakris GL. Review: Insulin and endothelin: An interplay contributing to hypertension development? J Clin Endocrinol Metab 2007;92:379–385.

23. French KR, Pollitt CC. Equine laminitis: Glucose deprivation and MMP activation induce dermo-epidermal separation in vitro. Equine Vet J 2004;36:261–266.

24. Nourian AR, Baldwin GI, van Eps AW, et al. Equine laminitis: Ultrastructural lesions detected 24–30 hours after induction with oligofructose. Equine Vet J 2007;39:360–364.

25. Muniyappa R, Montagnani M, Koh KK, et al. Cardiovascular actions of insulin. Endocr Rev 2007;28:463–491.

26. Muniyappa R, Iantorno M, Quon MJ. An integrated view of insulin resistance and endothelial dysfunction. Endocrinol Metab Clin North Am 2008;37:685–711, ix–x.

27. Mancia G, Bousquet P, Elghozi JL, et al. The sympathetic nervous system and the metabolic syndrome. J Hypertens 2007;25:909–920.

28. Leclercq IA, Da Silva Morais A, Schroyen B, et al. Insulin resistance in hepatocytes and sinusoidal liver cells: Mechanisms and consequences. J Hepatol 2007;47:142–156.

29. Cusi K, Maezono K, Osman A, et al. Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. J Clin Invest 2000;105:311–320.

30. Wyse CA, McNie KA, Tannahill VJ, et al. Prevalence of obesity in riding horses in Scotland. Vet Rec 2008;162:590–591.

31. Treiber KH, Kronfeld DS, Geor RJ. Insulin resistance in equids: Possible role in laminitis. J Nutr 2006;136:2094S–2098S.

32. Longland AC, Byrd BM. Pasture nonstructural carbohydrates and equine laminitis. J Nutr 2006;136:2099S–2102S.

33. Durham AE, Hughes KJ, Cottle HJ, et al. Type 2 diabetes mellitus with pancreatic b-cell dysfunction in 3 horses confirmed with minimal model analysis. Equine Vet J 2009. In press.

34. Tiley HA, Geor RJ, McCutcheon LJ. Effects of dexamethasone on glucose dynamics and insulin sensitivity in healthy horses. Am J Vet Res 2007;68:753–759.

35. Geor RJ, Hinchcliff KW, McCutcheon LJ, et al. Epinephrine inhibits exogenous glucose utilization in exercising horses. J Appl Physiol 2000;88:1777–1790.

36. Firshman AM, Valberg SJ. Factors affecting clinical assessment of insulin sensitivity in horses. Equine Vet J 2007;39:567–575.

37. Eiler H, Frank N, Andrews FM, et al. Physiologic assessment of blood glucose homeostasis via combined intravenous glucose and insulin testing in horses. Am J Vet Res 2005;66:1598–1604.

38. Bailey SR, Menzies-Gow NJ, Harris PA, et al. Effect of dietary fructans and dexamethasone administration on the insulin response of ponies predisposed to laminitis. J Am Vet Med Assoc 2007;231:1365–1373.

39. Murphy D, Reid SW, Graham PA, et al. Fructosamine measurement in ponies: Validation and response following experimental cyathostome infection. Res Vet Sci 1997;63:113–118.

40. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev 2005;26:19–39.

41. Toth F, Frank N, Martin-Jiménez T, et al. Measurement of C-peptide concentrations and responses to somatostatin, glucose infusion, and insulin resistance in horses. Equine Vet J 2010;42:149–155.

42. Schott HC II. Pituitary pars intermedia dysfunction: Equine Cushing's disease. Vet Clin North Am Equine Pract 2002;18:237–270.

43. Garcia MC, Beech J. Equine intravenous glucose tolerance test: Glucose and insulin responses of healthy horses fed grain or hay and of horses with pituitary adenoma. Am J Vet Res 1986;47:570–572.

44. Cottrell E, Watts K, Ralston S. Soluble sugar content and glucose/insulin responses can be reduced by soaking chopped hay in water. Proceedings of the Nineteenth Equine Science Society Symposium, Tucson, AZ. 293–298, 2005.

45. Longland AC, Barfoot C, Harris PA. The loss of water-soluble carbohydrate and soluble protein from nine different hays soaked in water for up to 16 hours. J Equine Vet Sci 2009;29:383–384.

46. Elliott J, Bailey SR. Gastrointestinal derived factors are potential triggers for the development of acute equine laminitis. J Nutr 2006;136:2103S–2107S.

47. Allen EM, Meyer W, Ralston SL, et al. Variation in soluble sugar content of pasture and turf grasses. Proceedings of the Nineteenth Equine Science Society Symposium, Tucson, AZ. 321–323, 2005.

48. Harris P, Bailey SR, Elliott J, et al. Countermeasures for pasture-associated laminitis in ponies and horses. J Nutr 2006;136:2114S–2121S.

49. Geor RJ, Harris P. Dietary management of obesity and insulin resistance: Countering risk for laminitis. Vet Clin North Am Equine Pract 2009;25:51–65, vi.

50. Houmard JA, Tanner CJ, Slentz CA, et al. Effect of the volume and intensity of exercise training on insulin sensitivity. J Appl Physiol 2004;96:101–106.

51. Bajpeyi S, Tanner CJ, Slentz CA, et al. Effect of exercise intensity and volume on persistence of insulin sensitivity during training cessation. J Appl Physiol 2009;106:1079–1085.

52. Johnson JL, Slentz CA, Houmard JA, et al. Exercise training amount and intensity effects on metabolic syndrome (from studies of a targeted risk reduction intervention through defined exercise). Am J Cardiol 2007;100:1759–1766.

53. Hawley JA. Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance. Diabetes Metab Res Rev 2004;20:383–393.

54. Powell DM, Reedy SE, Sessions DR, et al. Effect of short-term exercise training on insulin sensitivity in obese and lean mares. Equine Vet J Suppl 2002;34:81–84.

55. Stewart-Hunt L, Geor RJ, McCutcheon LJ. Effects of short-term training on insulin sensitivity and skeletal muscle glucose metabolism in standardbred horses. Equine Vet J Suppl 2006;36:226–232.

56. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.

57. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: Scientific review. JAMA 2002;287:360–372.

58. Frank N, Sommardahl CS, Eiler H, et al. Effects of oral administration of levothyroxine sodium on concentrations of plasma lipids, concentration and composition of very-low-density lipoproteins, and glucose dynamics in healthy adult mares. Am J Vet Res 2005;66:1032–1038.

59. Frank N, Elliott SB, Boston RC. Effects of long-term oral administration of levothyroxine sodium on glucose dynamics in healthy adult horses. Am J Vet Res 2008;69:76–81.

60. Frank N, Buchanan BR, Elliott SB. Effects of long-term oral administration of levothyroxine sodium on serum thyroid hormone concentrations, clinicopathologic variables, and echocardiographic measurements in healthy adult horses. Am J Vet Res 2008;69: 68–75.

61. Ramirez S, McClure JJ, Moore RM, et al. Hyperthyroidism associated with a thyroid adenocarcinoma in a 21-year-old gelding. J Vet Intern Med 1998;12:475–477.

62. Alberts MK, McCann JP, Woods PR. Hemithyroidectomy in a horse with confirmed hyperthyroidism. J Am Vet Med Assoc 2000;217:1051–1054.

63. Durham AE, Rendle DI, Newton JE. The effect of metformin on measurements of insulin sensitivity and beta cell response in 18 horses and ponies with insulin resistance. Equine Vet J 2008;40:493–500.

64. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest 2001;108:1167–1174.

65. Del Prato S, Bianchi C, Marchetti P. Beta cell function and anti-diabetic pharmacotherapy. Diabet Metab Res Rev 2007;23: 518–527.

66. Hustace JL, Firshman AM, Mata JE. Pharmacokinetics and bioavailability of metformin in horses. Am J Vet Res 2009;70:665–668.

67. Tinworth KD, Edwards S, Harris PA, et al. Pharmacokinetics of oral metformin in insulin-resistant ponies. Am J Vet Res 2010. In press.