UPDATE ON EQUINE METABOLIC SYNDROME

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Abstract

Equine Metabolic Syndrome (EMS) is not a disease itself, but rather a clinical syndrome associated with laminitis and characterized by three main components: obesity, insulin resistance (IR) and laminitis. Other components of this syndrome include hypertriglyceridemia, hyperleptinemia, arterial hypertension, infertility in mares and increased systemic markers of inflammation. EMS is most commonly recognized in young to middle aged horses (5-15 years of age), and owners typically refer to them as "easy keepers". Obesity is defined as increased regional or generalized adiposity characterized by the presence of fat pads. Basal hyperinsulinemia (insulin resistance) and/or excessive insulin response to either intravenous or oral glucose challenge (insulin dysregulation) are common findings.

It has been recognized that this syndrome results from an interaction between genetics and environmental factors. Environmental factors play an important role, with cases typically occurring usually in the spring during periods of rapid pasture growth. However the differences in susceptibility among horses managed in the same conditions may be a result of an underlying genetic predisposition.

It is important to recognize this syndrome based on clinical signs and be able to diagnose and adequately treat affected horses. It is also important to remember that obesity on its own does not necessarily mean the horse has EMS, but thin horses could also have EMS and be difficult to recognize. It is also important to recognize the difference between EMS and Pituitary Pars Intermedia Dysfunction (PPID), as they can occur simultaneously but need to be treated differently.

Keywords

EMS, Insulin resistance, obesity, laminitis, PPID

The term equine metabolic syndrome (EMS) was first introduced to veterinary medicine in 2002 when Johnson proposed that obesity, insulin resistance (IR), and laminitis were components of a clinical syndrome recognized in horses and ponies.[1] In 2010, the ACVIM Consensus Statement described EMS as a clinical syndrome, that has been defined as the presentation of a phenotype of obesity, insulin resistance and laminitis or a predisposition to laminitis in equids.[2]

Etiology

Obesity is defined as increased regional (e.g., cresty neck) or generalized adiposity. Obesity is the main risk factor for EMS and has been associated with increased morbidity and mortality in horses. Adipose tissue is an active endocrine organ secreting adipokines (leptin and adiponectin) and adipose-derived cytokines (TNF-α and IL-1) which can have adverse local and systemic effects. A scoring system for grading neck crest fatness has been recognized for a few years, and is known as the "cresty neck scoring system" on a scale of 0 to 5 where a score of zero equals no visual appearance of a crest and a score of five equals enormous and permanently drooping to one side.[3] Like the current overall body condition scoring system the cresty neck system is subjective and requires experience in learning to judge condition and practice to obtain consistent values. Even with these limitations the cresty neck scoring system has been proven to be a valuable tool when predicting a horse's risk of metabolic disease.

A small number of studies have attempted to determine the possible role of fat in the development of EMS. In horses, excess visible fat deposition occurs most commonly in the region of the neck crest and rump. Some researchers have suggested that neck crest adipose tissue is more active than omental adipose in horses, but the data are not conclusive.[4]

IR is characterized by basal hyperinsulinemia and/or an excessive insulin response to intravenous or oral glucose challenge (insulin dysregulation). 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).[5] Natural equine diets normally contain little fat, but when there is excess glucose it can be converted into fat. The concern is that when storage capacity of adipose tissue is exceeded, fats are repartitioned to skeletal muscle, liver and pancreas, where they can accumulate and alter normal cellular functions, including insulin signaling. It has been established that hyperinsulinemia will induce endocrinopathic laminitis in predisposed horses. The lesions in endocrinopathic laminitis are initially found in the secondary epidermal lamellae (SEL) including lengthening and narrowing, and developing tapered tips.[6]

IR and/or hyperinsulinemia predispose ponies to pasture associated laminitis. Insulin has vasoregulatory actions and it can be considered a 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. 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. The primary insult to the hoof in EMS is most likely due to alteration in the form and function of the vasculature, rather than inflammation, in contrast with laminitis secondary to systemic inflammatory response syndrome (due to grain overload, colic metritis, etc.).

Epidemiology
Breeds that appear to be more susceptible to EMS include Welsh and Shetland ponies, Morgan Horse, Paso Fino, Norwegian Fjord, Arabian, Saddlebred, Spanish Mustang, and warmbloods. 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.

A seasonal pattern has been identified for laminitis in the United States, with the highest incidence of pasture laminitis around April and June (late spring/early summer). This seasonal rise in laminitis incidence has been attributed to the increase in nonstructural carbohydrate (NSC) consumption from pasture forage. Pasture carbohydrate content and climate/seasonal effects are closely 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.[7]

There is a recent report suggesting that endocrine-disrupting chemicals (EDC) may play a role in the development of EMS. EDCs usually are human-made substances, found in products such as pesticides, plastics and personal care products. They are heavily prevalent in the environment and can mimic a body's hormones, blocking real ones from doing their jobs. Because of this, they are known to produce harmful effects in humans and wildlife. Horses likely come into contact with EDCs through their food. The team concluded that accumulation of EDCs may explain some environmental variance seen in horses with EMS, but the precise role and dose response to EDCs in horses with EMS is not clear at this time.[8]

Clinical Signs
Most commonly recognized 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. These protruding growth rings are wider at the heel than they are dorsally, and are thought to occur when laminitis inhibits dorsal hoof wall growth. Cresty neck scores ≥3 are commonly identified in horses and ponies with EMS. Abnormal regional adipose deposits in the tail head, prepuce or mammary gland area are also common. Body weight should be measured with a scale or weight tape and body condition scoring can be used to assess generalized obesity.

Diagnosis
It is very important to take into consideration the signalment of the horse. A complete history, physical examination, radiographs of the feet and laboratory tests are an integral part of the diagnostic process. Physical examination should include assessment of the horse for evidence of abnormal hoof growth or hoof soreness, regional adiposity, including adipose tissue expansion within the neck crest, and body condition scoring. Screening tests available are resting glucose, insulin and leptin concentrations.

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 high end of the reference range indicating partial loss of glycemic control. Elevated glucose levels can also be attributed to stress, recent feeding, administration of α-2 agonist drugs, or inflammatory processes.

Basal 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. Reference ranges vary among laboratories, but in general a value >20μU/ml is considered to be suggestive of IR. It is important to remember that cortisol and epinephrine released as a result of pain or stress lower tissue insulin sensitivity and raise resting glucose and insulin concentrations.[9]

Blood collection should be done after an approximately 6-hour period of feed withholding, ideally between 8:00 and 10:00 AM. These conditions can be achieved by providing no grain meals and not more than 1 flake of low-NSC grass hay per 500kg bodyweight no later than 10:00 PM the night before sampling. If it is not possible to obtain the horse under fasting conditions, or the horse is on pasture it is recommended to perform a dynamic insulin test.
Available dynamic insulin test include the oral glucose tolerance test, intravenous glucose tolerance test and a combined glucose-insulin test (CGIT). The CGIT is the preferred test if fasting samples are <20μU/ml, but IR is suspected.

Leptin is a hormone produced by adipocytes and has been associated with decreased insulin sensitivity. Elevated levels of leptin can be associated with increased body condition scores, but high levels alone do not mean the horse has EMS. Leptin levels are useful in tracking weight loss in obese horses. It is important to remember that draft and light draft type horses may have a higher normal range than light breed horses.

- Oral Sugar (Glucose) Test Procedure:
  Performed using corn syrup (Karo Light Syrup) which can be purchased and administered by the owner. 1ml of corn syrup provides 1g total glucose-based digestible carbohydrates. A dose of 0.15ml/kg or 15ml/100kg BW is administered orally through a dose syringe. A blood sample should be obtained 60-90 minutes post administration by the owner. This test should not be combined with simultaneous TRH stimulation test in horses suspected of having PPID.[10]

- CGIT Procedure:
  An intravenous catheter should ideally be placed the night before to minimize stress, which induces transient IR and will lead to a false positive result. A pre-infusion (baseline) blood sample is collected and then 150 mg/kg BW 50% dextrose solution (150 mL for a 500-kg horse) is quickly infused through the catheter, immediately followed by 0.10 units/kg BW regular insulin (100 units/mL; 0.50 mL for a 500-kg horse). Short-

acting recombinant human insulin or soluble porcine insulin should be used for this test. Blood samples are collected at 5, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135 and 150 minutes post infusion, but the test can be halted once the blood glucose level falls below baseline. Blood glucose concentrations are measured with a hand-held glucometer. Insulin concentrations should be measured prior to injection and at the 45 minutes post-injection time point. Both glucose and insulin responses to the CGIT are examined to interpret results.[11] There is a small risk of hypoglycemia developing in horses with higher insulin sensitivity, so two 60-mL syringes containing 50% dextrose should be kept on hand and administered if sweating, muscle fasciculations, or weakness are observed, or if the blood glucose concentration drops below 40 mg/dL.

Differentiating EMS from PPID

Both of these diseases can present with clinical signs of regional adiposity and laminitis. There are some characteristics that will help differentiate them, as they will need to be managed and treated differently.

- Age of onset: EMS affected horses are usually younger (5-15 years), while PPID affected horses are older >15 years. It is important that both of these disorders may occur concurrently.
- PPID affected horses will usually have other clinical signs including delayed winter coat shedding, hirsutism, polyuria and polydipsia and muscle mass atrophy, characterized by a loss of topline and a pot belly appearance.
- PPID affected horses will have elevated levels of adrenocorticotropic hormone (ACTH) in the absence of other confounding factors.
- The majority of PPID affected horses will have normal insulin sensitivity.

Treatment

1. - Diet

Management of **obese** horses is based on reducing caloric intake, increasing exercise (if no evidence of laminitis), and elimination of pasture access until the ideal body condition has been obtained. Until insulin sensitivity is normal, pasture access should be eliminated because carbohydrates consumed on pasture can trigger gastrointestinal events that lead to laminitis in susceptible horses.[12] All concentrates need to be eliminated and only hay with a low NSC content should be fed at 1.5% of ideal body. It is also recommended to add a ration balancer or a multivitamin/multimineral supplement to compensate the lower quality hay. Eliminate all treats containing sugar such as carrots, apples, peppermints, etc. The idea of this management practice is to target obesity and insulin resistance.

Management of the **lean** EMS horse aims to provide additional calories without exacerbating IR. These horses require feeds that are low in starch and sugar. It is recommended to feed smaller more frequent meals and also to feed hay 30 minutes before grain to minimize post feeding increases of insulin and glucose. Using soaked beet pulp (non molasses) will also provide

adequate amount of calories. Another possibility to supply calories to these horses is the use of corn and soy oils in their rations; 1 standard cup (225mL) of vegetable oil provides 1.7Mcal 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.[2]

Management of **IR in the obese** horse aims to control obesity through an adequate exercise program and avoiding feeds that will exacerbate IR. The majority of these horses will need to be in a "dry lot" until the IR is under control. Some horses may need to be permanently taken off pasture or have restricted access to pasture for no more than 1-2 hours per day. Using a grazing muzzle is also another option for these horses, but care must be taken that they are not overeating even with the muzzle on. Feeds that are low in starch and low in sugar are adequate, and all treats with sugar need to be eliminated. These horses should be carefully monitored and not allowed to graze new growth pasture in the spring or be on pastures that are stressed as the sugar contents on these will be very high.

Management of the **PPID and IR** horse involves the use of pergolide mesylate (Prascend®), a dopamine receptor agonist, and management of diet as needed depending on the level of IR that is present. In horses that have IR, highly soluble carbohydrate feeds should be avoided. Currently there are multiple commercial feeds that are appropriate for endocrine impaired horses, but the diet will need to be tailored individually based on the weight and hormonal changes. Medical management of PPID with pergolide typically improves insulin regulation in those horses affected by ID and it has been further proposed that pergolide might have an independent effect on insulin dynamics in horses.[6] Affected horses should be carefully monitored for IR and also for ACTH levels.

2. - Exercise

It has been demonstrated that exercise will not only induce weight loss, but also helps improve insulin sensitivity in both humans and horses. It is important that both exercise and dietary restrictions are followed to obtain the desired results in these obese horses.[13]

Horses that have an active acute or chronic laminitis episode will not be able to be exercised, until the horse is comfortable and not receiving any anti-inflammatories or analgesics. Corrective shoeing and adequate foot support are important prior to starting an exercise routine. Factors to consider will be the breed, level of fitness, and facilities available to the owner. Ideally these horses should be started on a soft surface for a short period of time (5-10 minutes per session) of longeing, and progressively be increased to about 15-20 minutes per session 2-3x/week. If the horse continues to be comfortable and no evidence of laminitis is present, the level of exercise can be gradually increased and the horse can be ridden 2-3x/week for 20-30 minutes, and then increased to 5 sessions/week. Each horse should be evaluated and an exercise routine should be individualized based on the response to exercise.

3. - Medical Management

Levothyroxine sodium (Thyro-L®)

- Should NOT be used in lean horses with EMS, as weight loss is not required

- Increases metabolic rate helping with weight loss. It helps by increasing insulin sensitivity, and decreasing body mass and neck circumference. Horses over 350Kg can have a dose of 48mg/day for 3-6 months. Smaller ponies and Miniature horses should receive a dose of 24mg/day. Once adequate weight has been obtained, horses will need to be weaned gradually over 4 weeks. Exercise and diet need to be an integral part of this regime.

Metformin hydrochloride (Glucophage®)

- Main mode of action is through inhibition of gluconeogenesis and glycogenolysis within the liver.
- Lowers blood glucose concentrations, and improves insulin sensitivity within tissues. Current recommended dose is 30mg/kg BID-TID
- Potential side effects include hypoglycemia and mild colic at the beginning or treatment. Stopping and then starting at a lower dose after a few days seems to improve the signs.

New Sodium-Glucose Transporter 2 (SGLT2) Inhibitors (Invokana®)

- Target receptors in the proximal tubule of the kidney to increase glucose loss in urine

Supplements and Nutraceuticals

-Chromium, magnesium, cinnamon, omega-3 fatty acids and chasteberry are commonly recommended, but there is not enough scientific evidence to support their use[14].

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