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Abstract

Insulin dysregulation is a factor in pituitary pars intermedia dysfunction and equine metabolic syndrome, both of which can lead to laminitis. In fact, the most common form of laminitis encountered in equine veterinary practice is hyperinsulinemia-associated laminitis, and postprandial hyperinsulinemia is thought to be the greatest risk factor for laminitis associated with insulin dysregulation. Thus, nutritional management of insulin dysregulation is central to minimizing the risk for laminitis. In some cases, medications may supplement nutritional management to treat severe insulin dysregulation and decrease the risk for laminitis; however, nutritional management remains the most effective therapeutic intervention for equine insulin dysregulation and should be implemented, in some form, for all patients.

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NUTRITION

Nutritional Management of Equine Insulin Dysregulation

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Obesity and its associated health complications in humans and veterinary species are epidemic in industrialized countries, and horses are no exception. Additionally, as horses are now routinely living into their third and fourth decades, the prevalence of diseases of aging—such as pituitary pars intermedia dysfunction (PPID), sometimes referred to as equine Cushing's syndrome—is also increasing.

Equine obesity and PPID are both associated with insulin dysregulation (ID), a state of disordered insulin and glucose dynamics that encompasses basal hyperinsulinemia, exuberant pancreatic response to carbohydrates, and tissue insulin resistance. Affected horses can display

1 or more of these abnormalities, and equine ID is pathophysiologically and contextually diverse. However, given the established link between hyperinsulinemia and laminitis, as well as the fact that *any* manifestation of ID can result in hyperinsulinemia, ID is an important point of intervention for therapy and prevention of laminitis in the setting of equine endocrine disease. Establishing a diagnosis and characterizing the severity of ID are essential to implementing and monitoring therapy, and the first line of therapy for mitigating hyperinsulinemia must be nutrition and diet management.

Take-Home Points

- Diagnoses of equine metabolic syndrome (obesity/regional adiposity, insulin dysregulation, and laminitis) and pituitary pars intermedia dysfunction are not mutually exclusive and require specific diagnostic tests to definitively diagnose and monitor treatment efficacy.
- The 3 principal goals of nutritional interventions for equine insulin dysregulation are to reduce dietary nonstructural carbohydrate content; limit meal size and rate of consumption; and, if needed, limit total caloric intake to facilitate weight loss.
- All diet components can influence postprandial insulin concentrations, including some not previously thought to be high-risk (e.g., ration balancers).
- A major therapeutic target for equine insulin dysregulation is dietary nonstructural carbohydrate content, which should be limited to no more than 10% on a dry matter basis of all diet components.
- For horses with insulin dysregulation that need to gain weight, the safest options for supplemental calories are fat and fiber.

ESTABLISHING A DIAGNOSIS

Diagnostic Testing for Insulin Dysregulation

ID is a clinicopathologic finding that can be observed in diverse clinical situations (e.g., obesity, sepsis, corticosteroid administration, endocrine disease); yet, in equine practice, ID is most often associated with equine metabolic syndrome (EMS). EMS is a collection

of clinical findings that includes hyperinsulinemia-associated laminitis (**FIGURE 1**), ID, and obesity (generalized or regional adiposity); together, these findings predict risk of future hyperinsulinemia-associated laminitis. Given the prevalence of EMS, signalment, physical examination findings, and clinical history can be highly suggestive of ID; however, definitive diagnosis requires specific screening and dynamic tests measuring glucose and insulin concentrations.¹

Initial diagnostic screening tests typically include measurement of basal glucose and insulin concentrations. However, many affected horses that exhibit abnormal insulin responses to dynamic challenge tests, as well as tissue insulin resistance, will demonstrate basal serum/plasma glucose and insulin concentrations that are consistently within laboratory reference ranges. The specificity of abnormal basal hyperinsulinemia is quite high, yet the sensitivity of this measurement is very low; values within the reference range do not rule out ID.² To accurately interpret the results of fasting measurements and facilitate repeatability for monitoring, the patient should not be offered feedstuffs with more than 10% nonstructural carbohydrates (NSC) within 6 hours of testing. Reference ranges depend on the analytical platform used by the diagnostic laboratory, and the corresponding laboratory's reference ranges should be used to interpret results (the same laboratory should be used for continued monitoring). However, basal insulin concentrations greater than 20 $\mu\text{IU/mL}$ (or the upper end of the reference range, which can vary, for the diagnostic laboratory being used) in the presence of euglycemia support a diagnosis of ID.

If basal insulin concentration is less than 20 $\mu\text{IU/mL}$ and other clinical or historical findings are indicative of ID, dynamic tests should be performed. Two feasible and economical dynamic tests that provide information about multiple facets of equine ID are the oral sugar test and the intravenous insulin tolerance test; ideally, both tests are performed to fully characterize insulin abnormalities. They are also useful for assessing the severity of ID, monitoring disease progression, and evaluating response to treatment.³

The preferred method for dynamic assessment of glucose and insulin concentrations in horses is the oral sugar test,³ which involves oral administration of light corn syrup (Karo Light at a dose of 15 mL [low dose⁴] or 45 mL [high dose⁵] per 100 kg [220 lb] of body



FIGURE 1. Lateral radiographic projections of the (A) left and (B) right forelimb digits of a 22-year-old American Paint Horse gelding with chronic hyperinsulinemia-associated laminitis secondary to equine metabolic syndrome and pituitary pars intermedia dysfunction. Note the rotation and distal displacement of the distal phalanx noted in both feet, as well as the very thin sole depth and long, overgrown toes.

weight) after a short period (4 to 6 hours) of withholding feed. A blood sample is collected at baseline and 60 and 90 minutes after sugar administration for measurement of glucose and insulin concentrations. An insulin concentration greater than 45 $\mu\text{IU/mL}$ (low dose) or greater than 60 $\mu\text{IU/mL}$ (high dose) at either time indicates abnormal hyperinsulinemia. Horse owners may be concerned about laminitis associated with the administration of glucose to animals with ID, but researchers who administered hundreds of oral sugar tests to horses and ponies for epidemiologic and genetic studies of EMS reported no new laminitis episodes immediately after testing⁶; the risk, therefore, seems to be quite low.

Another method for assessing tissue insulin sensitivity is the intravenous insulin tolerance test, which is convenient for on-farm clinical use (administered in 30 minutes, using 2 blood samples) and requires no dietary preparation. The test requires collection of a

baseline blood sample to measure glucose concentration with a handheld glucometer, administration of a dose of regular insulin (0.1 IU/kg IV), and collection of a second blood sample to measure glucose concentration 30 minutes later. A blood glucose concentration that does not decrease by 50% or more from baseline in response to insulin suggests systemic insulin resistance.⁷

Diagnostic Testing for Pituitary Pars Intermedia Dysfunction

PPID is the most common endocrinopathy of aged horses, and available data suggest that approximately 30% of horses with PPID also have ID. Given that ID seems to predict the severity of lamellar pathology in horses with PPID with laminitis and that horses with concurrent ID and PPID may be less likely to respond to conventional nutritional interventions (many of these horses are lean and may instead need to gain weight), early identification and treatment of PPID-



FIGURE 2. Images of a 26-year-old Thoroughbred mare with chronic hyperinsulinemia-associated laminitis associated with pituitary pars intermedia dysfunction. **(A)** The distal aspect of the mare's left forelimb, which has severe contracture of the superficial and deep digital flexor tendons. **(B and C)** Lateral radiographic projections of the forelimb digits. Note the rotation and remodeling of the distal phalanx in both feet, as well as the broken forward axis of both pasterns (RF > LF) associated with tendon contracture. The mare was treated with bilateral deep digital flexor tenotomies and was sound for pasture retirement postoperatively.



affected horses is useful for minimizing complications associated with ID (**FIGURE 2**). Severe or chronic PPID is typically not a diagnostic challenge because clinical signs alone can be highly suggestive. Hypertrichosis is considered pathognomonic for PPID, particularly in geriatric horses (18 years of age and older). However, the clinical presentation of PPID in younger horses (or those in early stages of the disease) can be more variable; diagnosis often relies heavily on diagnostic testing.⁸ Currently, assessment of endogenous adrenocorticotrophic hormone (ACTH) and thyrotropin-releasing hormone (TRH) stimulation test are the most reliable way to assess PPID.⁹

A good screening test for PPID is the measurement of resting ACTH concentration, although this value may fall within reference ranges in the early stages or in patients with mild disease. Healthy horses in the northern hemisphere exhibit higher ACTH concentrations in late summer and fall than in spring; thus, seasonally adjusted reference ranges have been established.⁹ To measure resting ACTH concentration, blood should be collected in EDTA-containing tubes and either kept chilled on ice before transport or centrifuged and frozen until harvested plasma can be analyzed. ACTH concentration tends to be lower in samples collected in glass tubes but this difference is minimal; overall, equine ACTH is more stable than previously believed. If a basal ACTH concentration supports a diagnosis of PPID, performing other more complex tests to confirm the diagnosis (e.g., TRH stimulation test) is not necessary.⁹

The TRH stimulation test is a dynamic test that may be more sensitive for detecting PPID during nonautumnal months than measuring ACTH concentration. There is no commercially available TRH product labeled for this use in horses; however, chemical-grade TRH can be diluted, filter-sterilized, and frozen in 1-mg aliquots until use. Veterinary compounding pharmacies can also prepare TRH as an injectable solution that is reasonably stable at room temperature.⁹ To perform a TRH stimulation test, a baseline blood sample should be collected, followed by intravenous administration of TRH (1 mg per horse or 0.5 mg per pony); an additional blood sample should be collected 10 minutes after TRH administration. Baseline and post-TRH samples should be submitted for measurement of ACTH concentrations. When testing is performed from January through June, ACTH concentrations higher than 100 pg/mL at 10 minutes after TRH administration suggest PPID.

Of note, because no seasonally adjusted reference ranges have been established for this test, it should be used only to identify negative cases between the months of July and December given the elevated risk for false-positive results obtained during this period. Adverse effects that may be observed in horses after TRH administration are yawning, lip movements, salivation, and trembling, which are usually mild and self-limiting; however, horse owners should be informed of them to minimize concern.

NUTRITIONAL MANAGEMENT OF EQUINE INSULIN DYSREGULATION

Role of Dietary Carbohydrates

Because dietary carbohydrate content is a central target of nutritional interventions for horses with endocrine diseases, defining the relevant carbohydrate fractions of a diet is necessary and will be estimated and reported in most proximate analyses of feedstuffs submitted to commercial laboratories (e.g., Equi-Analytical Laboratory Services, Ithaca, New York; equi-analytical.com).

NSC refers to carbohydrate components derived from plant cell contents, in contrast to components derived from plant cell walls (which are reported as neutral detergent fiber). NSC encompasses simple sugars, disaccharides, oligosaccharides, fructans, and starches. An NSC fraction contains the carbohydrates that are most likely to cause changes in insulin and glucose concentrations after consumption; therefore, this fraction is the target of most nutritional interventions for management of equine ID. Other ways of reporting components of NSC are ethanol-soluble carbohydrates (simple sugars, disaccharides, and oligosaccharides) and water-soluble carbohydrates (ethanol-soluble carbohydrate and fructans).¹⁰ All components of NSC should be measured and reported in any feedstuff offered to equine patients with ID.

Dietary Management Approaches

Diet management of EMS/ID involves the following 3 approaches.

Reduce NSC Content in All Components of the Diet

The first approach involves removing all cereal grains and concentrate feeds from the diet and selecting forage with an NSC content less than 10% on a dry matter

basis, which can be determined by submitting samples for proximate analysis. The relevance of NSC intake varies with the severity of the ID. Horses with severe ID (resting insulin concentration greater than 100 μ IU/mL) should be maintained on a stringent diet with an NSC content less than 10%, whereas mildly affected horses can likely be fed forages with an NSC content of 10% through 16%. If hay has already been purchased and the NSC level is greater than 10%, the hay can be soaked (**FIGURE 3**). Soaking hay in cold water for 1 to 2 hours before feeding can decrease the NSC content by up to 25%.¹¹ Protocols that use hay soaking alone (16 °C [61 °F] for 9 hours), steaming (50 minutes in a hay steamer) followed by soaking, or soaking followed by steaming all seem equally effective at reducing the NSC content of hay (by approximately 30%), although soaking followed by steaming resulted in the lowest levels of microbial contamination of the final product.¹² For ponies, soaked hay has been shown to induce lower postprandial insulinemic responses than dry hay or haylage,¹³ and feeding soaked hay has been associated with accelerated weight loss in overweight horses and ponies.¹⁴ Warmer soaking water can result in more effective NSC leaching from forage; however, this practice also accelerates microbial proliferation within the product, may cause hygienic problems with feeding,¹⁵ and may render the forage less palatable.¹⁶



FIGURE 3. Grass hay soaking in a hay net. This hay was soaked for 60 minutes in cold water to decrease its nonstructural carbohydrate content to make it more suitable for feeding to a horse with severe insulin dysregulation and hyperinsulinemia-associated laminitis. The water was disposed of in a place inaccessible to the horse and the hay was fed after 60 minutes of soaking. Uneaten soaked hay was removed after 2 hours to avoid unsanitary microbial proliferation.

Limit Access to Pasture and Slow Rate of Forage Consumption

The second approach involves removing the affected animal from pasture. Pasture grasses are a source of NSC of which consumption is difficult to quantify. Pasture content changes over time in response to growth phase, environmental stressors, and season (among other factors); therefore, carbohydrates in pasture grass can continue to exacerbate ID even when other aspects of the diet have been tightly controlled. Horses with recurrent laminitis may require housing away from pasture indefinitely. These animals should be housed in dirt paddocks so they can move freely and exercise after laminitis has been controlled. Mildly affected horses can return to pasture if their ID is well controlled, but their access should remain restricted when grass is going through predictable dynamic phases, such as rapid growth in the spring and initial cold stress in the fall. Grazing in the early morning is most likely safer for horses with ID except after a hard frost when grass accumulates sugars. Grazing muzzles can effectively control the rate of weight gain in ponies at pasture when worn for 10 hours per day, but individual responses vary significantly. Limiting forage intake by a slow-feed hay net extends the time for meal consumption and delays peak postprandial insulin concentration. Last, strip grazing practices result in decreased dry matter consumption and body weight gains compared with unlimited pasture access for ponies.¹⁷ Most of these techniques can improve the nutritional management of horses and ponies with ID.

Restrict Calories if Weight Loss Is Needed

The third approach involves improved body condition through weight loss. Weight loss should be encouraged for overweight or obese horses by restricting the total number of daily calories consumed. Removing all concentrate feed from the diet is often sufficient to achieve an ideal body weight for horses that are being overfed. Total caloric intake should initially be met by feeding hay in amounts equivalent to 1.5% to 2% of their current body weight. If a horse does not lose weight within 4 to 6 weeks, the amount fed should be gradually decreased over several weeks to 1.5% of ideal body weight. Feeding less than 1% of ideal body weight in forage per day may increase the risk for dangerous metabolic complications (e.g., hyperlipidemia) for patients with ID and should be avoided. These strategies are effective for horses kept in stalls or dirt paddocks, but weight loss is more difficult to achieve when horses graze on pasture.

Additional Considerations

Ration Balancers

Appropriate vitamin and mineral supplements should be provided to horses confined to dirt paddocks or stalls or whose daily forage ration consists of a restricted amount of grass hay. Although high-protein ration balancers have been used extensively for the management of equine ID historically, caution may be warranted as recent evidence suggests that they, too, can be associated with postprandial hyperinsulinemia in affected horses.¹⁸⁻²⁰ Ration balancer products with lower protein contents (12% through 15% crude protein) may be better options to decrease postprandial hyperinsulinemia. Further, patients receiving high-protein ration balancers whose ID is poorly controlled should have the ration balancer component of their diet critically evaluated; a low-protein vitamin and trace mineral supplement may be a better option.

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Lean Horses With Insulin Dysregulation

Management of lean horses with EMS can be challenging because more calories must be provided without exacerbating ID. Feeding a commercially available low-sugar/low-starch (low-NSC) pelleted feed can simplify the process; however, the NSC content of these feeds varies and the severity of ID must be considered when selecting a particular product. Additionally, dividing a daily ration into multiple small portions and feeding hay before offering concentrates slow gastric emptying. These strategies are used to lower the glycemic response to a meal, which is the degree to which blood glucose concentrations rise in

response to the feed. Individual horses may respond differently to the same feed; therefore, rechecking glucose and insulin concentrations 7 to 14 days after initiating a new diet is recommended. Management of severely affected horses can be particularly difficult and may require individual diet formulations with the help of an equine nutritionist. Rinsed and soaked molasses-free beet pulp can be fed as a more economical alternative to commercial feeds; it induces a low glycemic response yet provides calories through hindgut fermentation and volatile fatty acid production. Fat and fiber are safer sources of calories than NSC for horses with ID that need to maintain or gain weight.

Investigating the Role of Diet for Horses With Poorly Controlled Insulin Dysregulation

In managing poorly regulated ID despite an apparently tightly controlled, low-NSC diet, a feed trial can be performed to evaluate the degree of postprandial hyperinsulinemia in response to various components of the diet. Feed trials can be approached in much the same way as the oral sugar test, which is currently in widespread use for the diagnosis of equine ID. Briefly, the horse should be fed 1 flake of grass hay the night before the test, then muzzled until the test begins the next morning. A blood sample should be collected at baseline, and then the horse is fed the diet component (e.g., a meal of a ration balancer in the amount recommended by the manufacturer or amount already being regularly fed to the horse). Additional blood samples should be drawn at 30 and 60 minutes postprandially to evaluate the horse's insulinemic response to the feedstuff. Exaggerated insulinemic responses (suggested evaluative criteria could be greater than 45 μ IU/L at either time for horses with normal baseline insulin concentrations, or an increase of more than 30 μ IU/L of insulin concentration from an abnormal baseline concentration) should warrant modification of that portion of the diet (e.g., elimination, substitution, amount alteration).²⁰

SUMMARY

Hyperinsulinemia-associated laminitis is the most common form of laminitis in adult equine populations, and conditions associated with ID (e.g., EMS, PPID) underlie most cases. Diagnostic confirmation with laboratory testing is crucial to identifying early disease and monitoring response to therapy. Given the link between diet composition and insulin and glucose

dynamics, nutritional interventions are a critically important first-line therapy for mitigating hyperinsulinemia associated with ID. For all cases, these interventions should include modifying the diet to maintain a healthy body weight, limiting dietary NSC content to less than 10%, and engaging in strategic pasture management. If implemented consistently, these efforts may obviate the need for more intensive medical therapies. Equine ID is frequently a nutritional disease; thus, it should always include nutritional management. **TVP**

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CE QUIZ QUESTIONS

1. A diet for a patient with equine insulin dysregulation (ID) should ideally contain no more than _____ nonstructural carbohydrates on a dry matter basis.
 - a. 5%
 - b. 10%
 - c. 20%
 - d. 50%
2. Which of the following diet components influence equine postprandial glycemic and insulinemic responses?
 - a. Preserved forage (e.g., hay, haylage)
 - b. Cereal grains
 - c. High-protein ration balancers
 - d. All of the above
3. ID is one of the diagnostic criteria for equine metabolic syndrome (EMS). This general term incorporates more specific abnormalities in insulin and glucose dynamics, including basal hyperinsulinemia, acute pancreatic response to carbohydrate, and insulin resistance at the tissue level; these can be present or absent independent of each other, and not all patients display all of them. Ideally, all facets of ID are assessed when evaluating an EMS suspect; which of the following testing options would accomplish this goal?
 - a. Euglycemic-hyperinsulinemic clamp
 - b. Intravenous insulin tolerance test and oral sugar test
 - c. Combined glucose and insulin test
 - d. Oral sugar test with incretin response
4. Which of the following is the most sensitive test for equine pituitary pars intermedia dysfunction?
 - a. Basal endogenous adrenocorticotrophic hormone (ACTH) concentration, measured in February
 - b. Thyroid-stimulating hormone test
 - c. Basal ACTH concentration, measured in October
 - d. 19-hour dexamethasone suppression test
5. Which of the following might be helpful for making pasture access safer for a horse with ID?
 - a. Use of a grazing muzzle
 - b. Strip grazing
 - c. Early-morning grazing
 - d. All of the above

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