Endocrinopathic Laminitis, Obesity-Associated Laminitis, and Pasture-Associated Laminitis

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1. Introduction
In a recent online survey, we asked equine practitioners to list the three most common causes of laminitis in horses seen within their practice. We expected veterinarians to list colitis, colic, and retained placenta as the primary causes of laminitis, but many respondents listed obesity, insulin resistance (IR), equine metabolic syndrome (EMS), pituitary pars intermedia dysfunction (PPID), and lush pasture. These results reflect the prevalence of endocrine/metabolic problems in horses that are seen in general practice. We will examine these problems and discuss the potential mechanisms involved in endocrinopathic laminitis.

2. Terminology
Insulin resistance is defined as the failure of tissues to respond appropriately to insulin. There are numerous ways in which tissues become insulin resistant, including a reduction in the density of insulin receptors on the cell surface, malfunction of insulin receptors, defective internal signaling pathways, and interference with the translocation or function of glucose transporter 4 (GLUT4) proteins. Obese horses are more likely to suffer from IR, and insulin sensitivity decreases when obesity is experimentally induced. Insulin resistance can be diagnosed by measuring blood insulin concentrations, which are usually elevated in affected horses. We hypothesize that IR is the key determinant of laminitis susceptibility in horses, and this explains why specific animals within a herd develop disease. This hypothesis is supported by evidence that insulin-resistant ponies are more likely to develop pasture-associated laminitis and that laminitis can be experimentally induced by infusing insulin intravenously.

Obesity-associated laminitis is a useful term because obesity is easily recognized, and owners can address this issue to reduce the risk of laminitis. However, it has not been established whether obesity per se raises the risk of laminitis or whether the disease is caused by IR, which is more common in obese horses. Obesity and IR are associated in horses, but it is important to recognize that not every obese horse is insulin resistant. Some animals may be more tolerant of obesity, or it may take a certain period of time for IR to develop. Obese horses might also be more susceptible to laminitis because they are in a pro-inflammatory state. Obesity, inflammation, and IR are associated in humans because tumor necrosis factor α (TNFα) is secreted from adipose tissues as body mass index increases. This inflammatory cytokine inhibits insulin receptor signaling, which lowers insulin sensitivity. Vick et
al.\textsuperscript{5} found that blood TNF\textalpha{} mRNA expression was higher in obese horses, and our research group has detected elevated TNF\textalpha{} mRNA expression within adipose tissues collected from obese insulin-resistant horses.\textsuperscript{5} Insulin resistance may be the link between obesity and laminitis in horses, but systemic inflammation could also play a role in determining laminitis susceptibility.

Endocrinopathic laminitis is a general term that describes laminitis that develops in horses with endocrine/metabolic disorders. This includes laminitis that is associated with obesity, IR, PPID (also called equine Cushings disease), or corticosteroid administration.

EMS is a term that has been adopted to describe a clinical syndrome of obesity and/or regional adiposity, IR, and laminitis. This term is useful because it ties laminitis to IR. Grouping these problems together as a clinical syndrome prompts the practitioner to test for IR and make recommendations to control the problem. Horses of certain breeds and bloodlines are genetically predisposed to EMS. In our practice, Morgan horses, Paso Finos, Arabians, Tennessee Walking Horses, Warmbloods, and pony breeds are at higher risk, but this syndrome has been recognized in many other breeds. A more efficient energy metabolism seems to predispose animals to obesity and consequently IR. Young to middle-aged horses are affected, and there is an important interaction with management practices. Horses become obese and develop IR when they are fed too many calories in the form of grain or pasture grass.

PPID is the most common endocrinopathy affecting horses. Older horses are affected, and hirsutism is a key feature of this disorder. Hirsutism takes the form of a long curly haircoat in advanced cases, but delayed shedding of the haircoat is an early indicator of PPID. Skeletal muscle atrophy, polyuria, polydipsia, and laminitis are also clinical signs of this condition.\textsuperscript{6} More research is needed to determine whether horses with PPID are predisposed to laminitis because corticosteroid excess weakens hoof tissues over time or whether IR is the key determinant of laminitis risk in these patients.\textsuperscript{7} Johnson et al.\textsuperscript{7} reviewed the potential effects of systemic or local cortisol excess on laminar tissues and blood vessels.

Our experience suggests that horses with PPID that are also insulin resistant are more likely to develop laminitis than those with normal insulin sensitivity. Pergolide is the treatment of choice for PPID, and many horses respond positively to this drug. This positive response often includes improvement in insulin sensitivity because cortisol antagonizes the action of insulin and hyperadrenocorticism abates in treated animals. Not all patients with PPID suffer from IR. Insulin sensitivity seems to vary according to the body condition of the horse and stage of disease. Horses with PPID can have low, normal, or enhanced insulin sensitivity.

It is interesting to consider the idea of converging endocrinopathies. Horses that are initially obese and insulin resistant then develop PPID as they get older. A transition is sometimes observed in middle age (10–20 yr) as obese horses begin to retain their winter haircoat and start to lose skeletal muscle mass. Horses may be at the highest risk for endocrinopathic laminitis at this time.

Pasture-associated laminitis is also called grass founder and typically develops after the pasture grass grows rapidly in the spring or after a heavy rain. Pasture grazing contributes to obesity in metabolically efficient horses because large amounts of energy are consumed when grass is abundant. Sugars from pasture grass also exacerbate IR and contribute to the progression of this condition.\textsuperscript{1} It should also be recognized that lush pasture challenges the gastrointestinal tract because grass is consumed in large quantities over a relatively short period of time. This increases the mass of feed passing through the intestinal tract and therefore the total amount of carbohydrate entering the large intestine. The carbohydrate content and composition of the grass also varies markedly over time. Grass plants store carbohydrates when nutrients and sunlight are plentiful or when they are preparing for drought or winter conditions. Pasture grazing contributes to the development of obesity and IR and represents a dynamic factor that may trigger laminitis.

3. Relating IR to Laminitis

Vasoconstriction

Insulin possesses vasoregulatory properties, and this may explain why IR predisposes horses to laminitis. Slow vasodilation occurs in response to insulin through the increased synthesis of nitric oxide (NO) from endothelial cells.\textsuperscript{5} However, insulin also promotes vasoconstriction by stimulating the synthesis of endothelin-1 (ET-1) and activating the sympathetic nervous system.

Activation of the insulin receptor stimulates two different signaling pathways within the vascular endothelial cell. 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. The effects of insulin on glucose uptake are mediated by PI3K, so this pathway is disrupted when IR develops. Interestingly, this causes the MAPK pathway to be stimulated and ET-1 synthesis increases. Vasoconstriction is promoted in the insulin-resistant animal as NO production decreases, and this may impair the ability of vessels to respond to vascular challenges. Eades et al.\textsuperscript{9} detected an increase in plasma ET-1 concentration within blood collected from digital veins 12 h after carbohydrate was administered to induce laminitis in healthy horses. This finding suggests that digital vessels undergo vasoconstriction as a result of carbohydrate
overload in horses, which may contribute to the development of laminitis. If that is the case, horses with chronic IR would be more likely to develop laminitis when challenged, because IR has already promoted vasoconstriction.

Adhesion Molecules
These molecules are found on the surface of endothelial cells and may play an important role in the development of laminitis. Loftus et al.\textsuperscript{10} detected higher mRNA expression of intracellular adhesion molecule (ICAM) and E-selectin within laminar tissues collected 1.5 h after black walnut extract was administered to induce laminitis. Insulin stimulates the expression of vascular cell adhesion molecule (VCAM-1) and E-selectin through the MAPK pathway. When IR develops, the PI3K pathway is disrupted, which activates the MAPK pathway and further increases the abundance of adhesion molecules. The adhesion molecules ICAM and E-selectin facilitate neutrophil emigration into laminar tissues and therefore play a role in the development of laminitis.\textsuperscript{10} Horses with chronic IR may be more susceptible to laminitis because they have a greater abundance of adhesion molecules on the endothelial surfaces of laminar vessels. These horses may respond to inflammatory stimuli that other horses are able to tolerate.

Platelet Activation
Platelet accumulation and activation play a role in the development of laminitis in horses,\textsuperscript{11} and it is likely that chronic IR enhances these processes. Weiss et al.\textsuperscript{12} injected radioactively labeled platelets into ponies and detected platelet accumulation distal to the coronary band when nuclear scintigraphy was performed. Microthrombi were also detected in dermal veins. Studies performed by Bailey et al.\textsuperscript{11} and Menzies-Gow et al.\textsuperscript{13,14} have shown that endotoxin and vasoactive amines activate platelets and increase production of thromboxane and 5-hydroxytryptamine (5-HT). These platelet-derived mediators induce vasoconstriction, which reduces perfusion to the digit.\textsuperscript{13,14} The effects of obesity or chronic IR on platelet function have not been studied in horses or ponies, but IR reduces NO synthesis by endothelial cells in humans, and this vasodilator inhibits the aggregation of platelets.\textsuperscript{8} Insulin-resistant horses or ponies may not be able to withstand the vasoconstriction triggered by endotoxemia or the release of vasoactive amines from the intestine. These intestinally derived factors increase production of thromboxane and 5-HT by platelets and cause digital vasoconstriction.\textsuperscript{15} Digital arteries within the equine limb are 30–40 times more sensitive to vasoconstrictors such as serotonin, which suggests that platelet-derived mediators have more profound effects on the laminar blood supply.\textsuperscript{16,17} Laminitis may develop in the insulin-resistant animal because endothelial cells are unable to increase NO production to counteract vasoconstriction. It has been established that endothelial-derived NO modulates the response to vasoconstrictors within the vasculature of the equine digit.\textsuperscript{18}

Capillary Recruitment
Chronic IR may have other effects on the vasculature because insulin is involved in capillary recruitment.\textsuperscript{8} In humans, ingestion of a meal is associated with increased blood flow to limbs and decreased vascular resistance.\textsuperscript{19} Terminal arterioles dilate, which increases the number of capillaries that are perfused. This is referred to as capillary recruitment, and it is a physiologic mechanism that enhances glucose delivery to myocytes.\textsuperscript{8} In one study performed in humans, microvascular volume within the forearm increased by 45% 1 h after eating a meal.\textsuperscript{19} IR impairs the process of skeletal muscle capillary recruitment and contributes to the development of hyperglycemia in humans.\textsuperscript{20} It is conceivable that capillary recruitment also occurs within the vasculature of the equine foot. The digital circulation of the foot is complex in horses and includes arteriovenous anastomoses.\textsuperscript{21} These anastomoses may be affected by chronic IR.

4. Relating Obesity to Laminitis
Obese horses are more likely to develop laminitis if they are insulin resistant, but obesity itself may also contribute to laminitis susceptibility. In other species, obesity is associated with increased free fatty acid (FFA) concentrations, altered adipokine production by adipose tissues, and elevated levels of inflammatory cytokines within the blood.\textsuperscript{22} It should also be recognized that obese horses carry more weight on their hooves, which increases the forces exerted on dermoeidermal attachments.

Nutrient excess and increased FFA flux into tissues induces both IR and inflammatory responses that are both mediated by Toll-like receptor 4 (TLR4).\textsuperscript{23} As the movement of free fatty acids into tissues increases, skeletal myocytes accumulate lipids such as diacylglycerols, and this interferes with insulin signaling. This process of lipotoxicity results in IR but does not occur in all cases because individuals vary with respect to genetic susceptibility. A pro-inflammatory state is created as obesity progresses and more monocytes enter adipose tissues in response to monocyte chemoattractant protein-1 (MCP-1). This increases the number of macrophages within adipose tissues and the amount of TNFα secreted.\textsuperscript{23} TNFα impairs NO-mediated vasodilation, increases ET-1 production, and stimulates the expression of the adhesion molecules ICAM-1, VCAM-1, and E-selectin. Interleukin-8 is also stimulated, so neutrophil production and emigration tissues are enhanced by higher blood TNFα concentrations.\textsuperscript{22}

Obesity also affects adipokine production, and this can impact the body as a whole. Adipokines are hormones produced by adipocytes that have local
(paracrine) and remote (endocrine) effects on tissues. Leptin and adiponectin are the most well-known adipokines, and obesity has been associated with higher plasma leptin levels and lower plasma adiponectin concentrations in horses. Adiponectin enhances insulin sensitivity, so lower plasma concentrations are also associated with IR. Endothelium-dependent vasodilation may also be compromised when adiponectin concentrations are low, and this might contribute to the pro-inflammatory state induced by obesity.

Obesity is likely to predispose horses to laminitis by many of the same mechanisms as IR, which suggests that these factors combine to lower the threshold for disease. The obese horse with IR is likely to have a low threshold for laminitis, which explains why the disease can be triggered more easily in these animals.

5. Triggers for Laminitis

It is relatively easy to understand why a horse with bacterial colitis develops laminitis because endotoxemia causes systemic inflammation and affects blood pressure, peripheral perfusion, endothelial cell function, and coagulation. However, it is much harder to understand why laminitis develops in apparently healthy horses that are kept on pasture or in stalls.

Researchers at Virginia Tech University have studied the predisposing factors for pasture laminitis and shown that insulin-resistant ponies are more likely to develop disease. However, the actual triggers for pasture-associated laminitis must still be determined. There are two theories that may explain the triggering of laminitis: (1) an IR crisis occurs or (2) alterations in the gastrointestinal microbial flora trigger laminitis.

IR Crisis

This theory is supported by results of recent study in which Asplin et al. induced laminitis in clinically normal ponies by infusing insulin and glucose IV for up to 72 h. Intravenous infusion of insulin caused profound hyperinsulinemia in the five treated ponies, and the mean time for laminitis to develop was 33 h. It should be noted that the mean ± SD serum insulin concentration was 1,036 ± 55 IU/ml in treated ponies, which far exceeds levels detected in horses seen in our practice before laminitis developing. However, healthy non-obese ponies were selected for study, so it can be argued that the degree of hyperinsulinemia necessary to induce laminitis may be much lower in susceptible animals with chronic IR.

If laminitis can be triggered by exacerbation of IR and hyperinsulinemia, this explains why horses kept in stalls spontaneously develop disease. It is likely that several factors combine to trigger laminitis in these animals. First, the affected horse may be suffering from chronic IR as a result of obesity, and this condition has progressed over time. As the horse ages, PPID is more likely to develop and this exacerbates IR and enhances the effects of season on glucose and insulin metabolism. These factors layer on top of each other and may trigger laminitis once a certain threshold has been reached. Changes in diet represent another layer and this factor can have a profound effect on insulin sensitivity in the chronically insulin-resistant horse. Laminitis can be triggered by simply feeding a sweet feed that is rich in sugar to a chronically insulin-resistant horse.

Horses kept on pasture may be affected by the same cluster of factors as horses kept in stalls—chronic progressive IR, development of PPID, and seasonal changes in hormones and energy metabolism. However, these animals must also contend with dynamic dietary challenges. The grass consumed by horses on pasture changes in total mass available, sugar content, carbohydrate profile, and protein composition over time. These changes can exacerbate IR, and laminitis may be triggered when IR goes beyond a certain threshold level for the individual horse or pony.

Triggers From the Intestine

The second theory identifies the intestine as the source of laminitis triggering factors. Laminitis has been experimentally induced by creating a situation of carbohydrate overload within the large intestine. This is accomplished by administering oligofructose or a mixture of cornstarch and wood flour directly into the stomach using a nasogastric tube. Both approaches accomplish the same goal of altering the microbial flora, enhancing lactic acid production, lowering the intraluminal pH, and increasing intestinal permeability. Exotoxins, endotoxins, vasoactive amines, or other bacterial by-products subsequently move into the blood and initiate a systemic inflammatory response that triggers laminitis. The events after carbohydrate administration are similar for both models—the horse exhibits clinical signs consistent with endotoxemia including tachycardia, fever, and abdominal discomfort, which is followed by laminitis. Sprouse et al. detected elevated plasma endotoxin concentrations after carbohydrate overload, suggesting that endotoxemia is associated with the development of disease. However, it is also possible that endotoxemia simply reflects an increase in intestinal permeability and vasoactive amines are the factors that trigger disease. Endotoxemia and laminitis have been associated in a retrospective study of hospitalized horses, but the disease has never been induced by administering exogenous lipopolysaccharide to horses.

Pasture-associated laminitis can be explained by this theory by recognizing that pastured horses are subjected to carbohydrate overload as grass grows rapidly and sugars accumulate. However, it is harder to explain why the horse kept in a stall develops laminitis, particularly if the diet has remained constant over time. According to the intestinal theory, this situation would be explained by an
alteration in microflora and/or intestinal permeability that is not detected by the horse owner. Rodents, birds, or other wildlife entering the stall may serve as a source of bacteria or perhaps mycotoxins within the hay or grain trigger intestinal disturbances. More testing should be performed to try and identify these intestinal disturbances instead of simply labeling them as idiopathic laminitis cases. Unfortunately, this is complicated by the fact that intestinal disturbances usually precede clinical laminitis by several days.

6. Evaluating the Horse With Endocrinopathic Laminitis

It is important to recognize that the pain associated with laminitis stimulates cortisol and catecholamine release, and this exacerbates IR. Consequently, false-positive results are more likely if testing is performed when the horse is still painful as a result of laminitis. It is therefore necessary to delay testing until after the pain of laminitis has subsided. This confounding factor may also explain why horse owners misinterpret responses to supplements that are administered to increase insulin sensitivity. Any supplement will seem to be effective if the pre-treatment blood sample is collected when the horse is painful and the pain subsided over time.

Horses should be evaluated by examining physical characteristics. Body condition scoring should be performed, and the horse should be examined for adipose tissue deposits within the neck and other regions. IR should be suspected if a “creasy neck,” enlarged fat pads close to the tailhead, or adipose deposits within the prepuce or mammary regions are detected.\(^3\)

All horses with a history of laminitis should be screened for IR, and this is easily accomplished by measuring serum insulin concentrations. Once the pain of laminitis has subsided, the horse should be kept in a stall and fed only hay overnight. A blood sample should be collected the next morning. Reference ranges should be established for the laboratory used and ideally for the horses on the farm. When using our laboratory, we consider a serum insulin concentration >30 \(\mu\text{U/ml}\) to be elevated (hyperinsulinemia) and therefore indicative of IR. Concentrations between 20 and 30 \(\mu\text{U/ml}\) may also indicate IR if the age, breed, and physical status of the horse are considered. Serum insulin concentrations can be measured as a screening test, but some horses with the IR phenotype have insulin levels that fall within the reference range. A diagnosis of IR can only be reached by performing a challenge test in these animals, and the combined glucose-insulin test (CGIT) is recommended for this purpose.

It is more difficult to confirm the diagnosis of PPID in horses, particularly when the disorder is just beginning to develop. Owners should watch for signs of delayed haircoat shedding or shifts in metabolism. A horse that has been obese when only fed a small amount of grain may start to require more calories as PPID develops. Measuring plasma adrenocorticotropin hormone (ACTH) concentrations is the easiest method of detecting PPID, but levels are elevated in response to pain, and this test will only identify advanced disease. The dexamethasone suppression test (DST) is another option, but owners may be concerned about the risk of exacerbating laminitis. An oral domperidone challenge test has recently been developed and seems to be the best method of detecting early PPID.\(^3\) This test is recommended because it is easy to perform and results have been correlated with pituitary lesions.

7. Managing the Horse With Endocrinopathic Laminitis

The two principal strategies for addressing IR in horses are (1) to induce weight loss in obese horses and (2) to improve insulin sensitivity through dietary management (and exercise). Obese horses should be placed on a weight reduction diet composed of hay and a vitamin and mineral supplement. Horses should initially receive hay in an amount equivalent to 1.5% of their current body weight per day (18 lb of hay for a 1200-lb horse), and this amount should be lowered to 1.5% of ideal body weight (15 lb for a 1000-lb horse) over 2 wk. The weight reduction diet should be continued until an ideal body condition score has been attained. Grain or pellets should be completely eliminated from the diet, and there should be no access to pasture during the weight loss period. Analysis of hay is strongly recommended to ensure that the non-structural carbohydrate (NSC) content is low. Samples can be sent to the Dairy One Forage Laboratory (1–800-496–3344), and the cost of analysis is approximately $30 per sample. Hay with an NSC level (ethanol soluble carbohydrate + starch) <10% as-fed should be selected for affected horses. If the horse owner can only find hay with a higher NSC level, soaking for 30 min in cold water is recommended to reduce the sugar content without leaching out other nutrients. Obese horses should be exercised as soon as hoof structures have stabilized. Exercise is likely to increase the rate of weight loss and improve insulin sensitivity.

In certain situations when obesity and IR persist despite dietary interventions, weight loss can be accelerated by administering levothyroxine sodium\(^2\) at a dosage of 4 teaspoons (48 mg) orally once daily for 3–6 mo. Levothyroxine reduces body fat mass and improves insulin sensitivity in horses that are kept off pasture and maintained on a controlled diet.\(^31,32\) Treated horses should be weaned off the drug once the ideal body weight has been attained by reducing the dosage to 2 teaspoons (24 mg) orally per day for 2 wk and then 1 teaspoon (12 mg) orally per day for 2 wk.

Leaner horses with IR should be fed hay and a commercial low-starch or low-NSC pelleted feed. The hay component of the diet should be as high as possible, and serum insulin concentrations should ideally be monitored after the pelleted feed has been
provided for 2 wk because individual horses vary markedly in their responses to different feeds. Insulin-sensitizing drugs including metformin and supplements such as chromium and magnesium are being evaluated as treatments for IR in horses, but results of recent studies are not available yet.

References and Footnotes


