

The Big Step

BY AMANDA DUCKWORTH

NO HOOF, NO HORSE remains as true as ever, and while most of the headline-making laminitis stories in horse racing tend to relate to cases stemming from injury or illness—think Barbaro (unfortunate outcome) or Country House (positive outcome)—owners also need to be aware of the dangers of endocrinopathic laminitis.

This slow-onset variety of laminitis can result from conditions such as pituitary pars intermedia dysfunction (PPID)—which is commonly referred to as equine Cushing’s disease—or equine metabolic syndrome (EMS) as well as overconsumption. It is an all-too-common issue in horses.

Laminitis continues to be a highly researched area of veterinary medicine due to its detrimental effect on horses as well as its multiple etiologies.

“Paradigm shifts in understanding equine laminitis,” which was published in the January 2018 edition of the *Vet-*

erinary Journal, looked at progress that has been made in recent years as well as what the future might hold.

Examining endocrinopathic laminitis

“Laminitis, one of the most debilitating conditions of all equids, is now known to be the result of several systemic disease entities,” explained the review. “This finding, together with other recent developments in the field of laminitis research, has provoked a rethink of our clinical and research strategies for this condition.

“First, laminitis is now considered to be a clinical syndrome associated with systemic disease (endocrine disease, sepsis or systemic inflammatory response syndrome, SIRS) or altered weight bearing rather than being a discrete disease entity. Next, laminitis associated with endocrine disease (endocrinopathic

laminitis) is now believed to be the predominant form in animals presenting (primarily) for lameness.”

The terms laminitis and founder are often used interchangeably, but as the American Association of Equine Practitioners notes, acute laminitis refers to symptoms associated with a sudden initial attack, including pain and inflammation of the laminae, while founder is meant to describe the chronic condition associated with rotation of the coffin bone.

One of the best ways to keep hooves in good order is to regulate what is going in a horse’s body. Fear of founder is real, and often times it is caused when a horse overindulges on grain or because the lush spring grass has proved too tempting to an easy keeper.

In the February 2019 issue of the *Journal of Veterinary Internal Medicine*, the European College of Equine Internal Medicine issued a consensus statement concerning EMS and laminitis.

“EMS is a widely recognized collection of risk factors for endocrinopathic laminitis,” the statement reads “The most important of these risk factors is insulin dysregulation (ID). Clinicians and horse owners must recognize the presence of these risk factors so that they can be targeted and controlled to reduce the risk of laminitis attacks. Diagnosis of EMS is based partly on the horse’s history and clinical examination findings, and partly on laboratory testing.

“Several choices of test exist which examine different facets of ID and other related metabolic disturbances. EMS is controlled mainly by dietary strategies and exercise programs that aim to improve insulin regulation and decrease obesity where present. In some cases, pharmacologic aids might be useful. Management of an EMS case is a long-term strategy requiring diligence and



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Barbaro, winner of the 2006 Kentucky Derby, had an unfortunate outcome with laminitis



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MESSAGE FROM THE GRAYSON-JOCKEY CLUB RESEARCH FOUNDATION

THE LATEST ON LAMINITIS STUDIES



Grayson-Jockey Club
Research Foundation

BY DR. TERESA BURNS

LAMINITIS IS A CRIPPLING disease of equids that represents a major cause of economic loss and humane concern in equine populations worldwide. It is a critically important priority for equine research due to the high incidence of the disease (annual incidence of 2–7% of horses in recent studies), the pain induced by the condition (often resulting in euthanasia or loss of use), and the lack of effective therapies for treating it.

While laminitis can be a complication of several diverse conditions in equids (including colic, diarrhea, pneumonia, and severe lameness), endocrine disease (such as equine metabolic syndrome and PPID) is by far the most common underlying cause of laminitis worldwide today, accounting for almost 90% of laminitis cases attended by equine veterinarians. Similar to human metabolic syndrome, equine metabolic syndrome is now known to affect not only obese animals, but also horses maintained in ideal body condition for their occupation or breed. Abnormalities of insulin and glucose dynamics (commonly referred to as ‘insulin dysregulation’ or ID) have a strong association with lamellar injury and are a primary therapeutic target for equine patients with endocrinopathic laminitis.

Nutritional management and aerobic exercise are central to treatment of EMS, but both can be difficult in the face of refractory ID and the severe pain of laminitis, especially in genetically predisposed breeds (such as ponies, Arabians, and gaited breeds, for example). Thus, in addition to dietary and exercise management, it is critical to establish medications that improve ID in animals at risk for or already suffering from endocrinopathic laminitis; drugs that both improve systemic ID and protect the digital lamellae are particularly attractive prospects.

Many of the drugs available for treating ID activate important metabolic signaling pathways, such as a protein called

AMPK (5'-adenosine-monophosphate-activated protein kinase) that is present in virtually all cells of the body. This protein has been referred to as “exercise in a bottle,” and drugs that activate it might be particularly useful for improving ID in foundered horses that can't work due to foot pain. These drugs are used extensively in human medicine to treat metabolic syndrome and type II diabetes (metformin is an example), where they improve insulin and glucose dynamics.

Further, activation of AMPK has been shown to support the health of epithelial cells and foster the connections between them; these are the very cells that are critical for providing the strength of the equine digital lamellae in supporting the weight of the horse (and that fail in the setting of laminitis). AMPK is therefore an attractive therapeutic target in endocrinopathic laminitis, but few drugs that activate this enzyme have been critically evaluated in horses for this purpose, particularly when used in combinations. Several of them, however (such as aspirin, metformin, and resveratrol), have been safely used in horses for other purposes and are available on the market for veterinary use.

Our laboratory is interested in identifying drug therapies that are safe and effective for the treatment and prevention of equine ID and endocrinopathic laminitis. In a study supported by the Grayson Jockey Club Research Foundation, our research team has recently shown that two AMPK-activating drugs, metformin and aspirin, act synergistically

(greater effect than either drug alone) to improve insulin and glucose dynamics when administered as a combination to adult light-breed horses with dexamethasone-induced ID. Resveratrol, another AMPK-activating drug that acts like metformin and aspirin, would be another attractive therapeutic option for equine ID, given that resveratrol is safe, palatable, and economical, with products already on the market. It also might be even more effective against ID when given in combination with metformin and aspirin, but this hasn't been evaluated in horses to date.

In a follow-up study supported by GJCRCF, we plan to evaluate resveratrol, aspirin, and metformin combinations in the same model of dexamethasone-induced ID. If resveratrol further enhances the ability of the metformin/aspirin combination to improve ID, this will provide support for a novel combination medical approach; if resveratrol given alone is as effective as the metformin/aspirin combination, then a simplified approach using only one medication (that is also palatable and well-tolerated) might be feasible.

We are hopeful that this work will result in the establishment of a novel therapeutic protocol involving safe and economical medications, given easily by mouth, which can improve insulin and glucose dynamics in horses with ID. These drugs will then be another tool that enhances our ability to prevent endocrinopathic laminitis in horses at risk, treat laminitis in horses already suffering from it, and improve the health and well-being of the horse. **BH**

Dr. Teresa Burns is an assistant professor of equine internal medicine at The Ohio State University College of Veterinary Medicine.

discipline by the horse's care-giver and support and guidance from its veterinarians."

The link between hyperinsulinemia—too much insulin—and laminitis was recently examined in the study "Association between hyperinsulinemia and laminitis severity at the time of pituitary pars intermedia dysfunction diagnosis," which appeared in the January 2019 issue of *Equine Veterinary Journal*. It found that owners often were not aware of the issue.

"Hyperinsulinemia is the suspected component of insulin dysregulation having the strongest association with laminitis and occurs variably in equids with pituitary pars intermedia dysfunction (PPID)," explains the study.

For the study, serum insulin concentrations, owner-reported laminitis history, and radiographic evidence of laminitis were determined in 38 client-owned horses and ponies with confirmed PPID. The severity of their laminitis was divided into four categories—nonlaminitic, mild, moderate, and severe—based on the degree of distal phalangeal rotation.

Laminitis was reported by the owners of 37% of the equines, but, in fact, 76% were laminitic based on the study criteria.

"Although radiographic abnormalities were present in most animals at the time of PPID diagnosis, chronic laminitis remained unrecognized by many owners," the study found. "Owner awareness of laminitis increased with severity of hyperinsulinaemia and higher insulin concentrations were detected in association with more severe radiographic changes."

The fact endocrinopathic laminitis can sometimes go undetected by owners was also examined in the study "Phenotypic, hormonal, and clinical characteristics of equine endocrinopathic laminitis," which was published in the May 2019 issue of

the *Journal of Veterinary Internal Medicine*.

"Equine laminitis is an important disease affecting the attachment of the distal phalanx to the inner hoof wall, and the endocrinopathic form of the disease occurs most commonly," explains the study. "Although previous research has focused on the inflammatory forms of the disease, recent data support that endocrinopathic laminitis is a worldwide welfare issue that is presented to equine practitioners reasonably frequently.

"Currently, data on the clinical features of laminitis specific to the endocri-

nopathic form of the disease are limited, and owners might fail to recognize the disease, particularly in early or mild cases."

In all, 301 cases of laminitis were included in the study, which looked at ways to improve the risk assessment capabilities of clinicians and to inform on management strategies for this particular form of laminitis.

After being given consent by the owner, veterinarians provided information on horses that had been diagnosed with the disease, and serum insulin and plasma adrenocorticotrophic hormone concentrations were measured in each case.

Cases from Australia, Germany, New Zealand, the United Kingdom, and the United States were included, and they covered a wide variety of breeds, including Thoroughbreds. Just more than half of the cases that were studied were of horses that had experienced a previous episode of laminitis, which relates back to the belief that endocrinopathic laminitis carries with it a high risk of recurring.

"Concurrent EMS and PPID resulted in higher basal insulin concentrations than if an animal had a single underlying cause for their laminitis," the study found. "The insulin concentration was negatively correlated with the animal's height, being higher in ponies than horses and was positively correlated with their grade (severity) of laminitis."



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Country House, the 2019 Derby winner, has overcome laminitis

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This information helps explain the disease, as horses with concurrent endocrinopathies have more marked hyperinsulinemia and as such are potentially at a greater risk of suffering an episode of laminitis.

“Furthermore, by positively correlating basal insulin concentration with a measure of laminitis severity, this study has contributed to the knowledge that insulin concentration is integral to endocrinopathic laminitis,” concludes the study. “Careful management of hyperinsulinemia should be of paramount importance when treating a horse/pony with endocrinopathic laminitis.”

The premise endocrinopathic laminitis leaves horses vulnerable to relapse was examined in the study “Incidence and risk factors for recurrence of endocrinopathic laminitis in horses,” which appeared in the 2019 May issue of the *Journal of Veterinary Internal Medicine*.

A total of 317 privately owned horses and ponies with acute laminitis were considered for the study, and 276 equines with endocrinopathic laminitis were followed through to the study’s completion.

The study, which aimed to determine the incidence of, and risk factors for, the recurrence of endocrinopathic laminitis, collected data on veterinary-diagnosed cases of acute laminitis for two years, and each case was classified as endocrinopathic or non-endocrinopathic. After the initial acceptance into the study, follow-up data were regularly collected to determine whether laminitis reoccurred within two years of the diagnosis.

“The recurrence rate for endocrinopathic laminitis was 34.1%,” the study found. “The risk of recurrence during the two-year study period increased with basal, fasted serum insulin concentration, with the probability of recurrence increasing markedly as the insulin concentration increased beyond the normal range (0–20 μ IU/mL) to over the threshold for normal (up to approximately 45 μ IU/mL). Being previously diagnosed with laminitis was also a risk factor for recurrent laminitis. Cases with a higher Obel grade of laminitis were likely to recur sooner.

“Knowing that hyperinsulinemia and being previously diagnosed with laminitis are significant risk factors for recurrence will enable clinicians to proactively address these factors, thereby potentially reducing the risk of recurrence of laminitis.”

The Obel grading system is the most widely accepted method veterinarians use to describe the severity of a case of laminitis. Dr. Niles Obel created the system and described it in his PhD thesis *Studies of the Histopathology of Acute Laminitis*, which was published in 1948.

The system features different grades, with grade 1 being the lowest and grade IV being the highest. Lameness is not evident at a walk at grade 1, but by grade IV, horses express marked reluctance or absolute refusal to move.

Clearly, identifying a horse’s level of pain is subjective, but it does help veterinarians communicate each horse’s clinical issues while creating a benchmark for whether they are improving or deteriorating.



ANNE M. EBERHARDT

Laminitis is a highly researched area of veterinary medicine

In June 2019, *PeerJ* published “A ‘modified Obel’ method for the severity scoring of (endocrinopathic) equine laminitis,” which examined how to grade cases that were specifically endocrinopathic-related, as opposed to sepsis or injury-related.

“Endocrinopathic laminitis is now the most common form of the disease, and clinical signs may be mild, or spread across two Obel grades,” the study explains. “Overall, this study showed that both the Obel method and the new ‘modified Obel’ method had excellent agreement, reproducibility, and repeatability, when tested by 28 experienced equine veterinarians using 15 video recordings of endocrinopathic laminitis of varying severity (and normal animals).

“This study has shown that the ‘modified Obel’ method has excellent repeatability and reproducibility when used to severity score endocrinopathic laminitis cases from both a laminitis induction study and naturally occurring cases. The ‘modified Obel’ method is proposed for use in clinical laminitis trials, as a three-step examination that can allocate a severity score from 0-12 using individual clinical criteria. Future development of the ‘modified Obel’ method will include its validation in tracking recovery from laminitis in clinical trials.”

Overall, the need to understand laminitis better remains a mission of veterinarians and owners around the globe. As more is understood, horses have a better chance of avoiding or surviving the feared diagnosis, but owners also must be aware of best practices.

“Chronic laminitis is the primary, day-to-day effect of EMS—and also the most life-threatening, if not controlled,” states Dr. Emily A. Graves in her paper “Equine Endocrine Diseases: The Basics” for the AAEP. “As with PPID-affected horses and ponies, making a team of people to manage EMS-associated laminitis is critical.

“Owners must maintain strict control of dietary management and be prepared for acute laminitis episodes during season changes (especially spring pasture) and any disruption to his/her horse’s typical daily diet. Managing a horse or pony with EMS requires a long-term commitment but can be very successful.”

Laminitis will continue to be one of the most studied issues in hoof care, and that research is invaluable in the fight against it. **BH**

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