GUIDE TO INSULIN RESISTANCE & LAMINITIS

FOR EQUINE PRACTITIONERS

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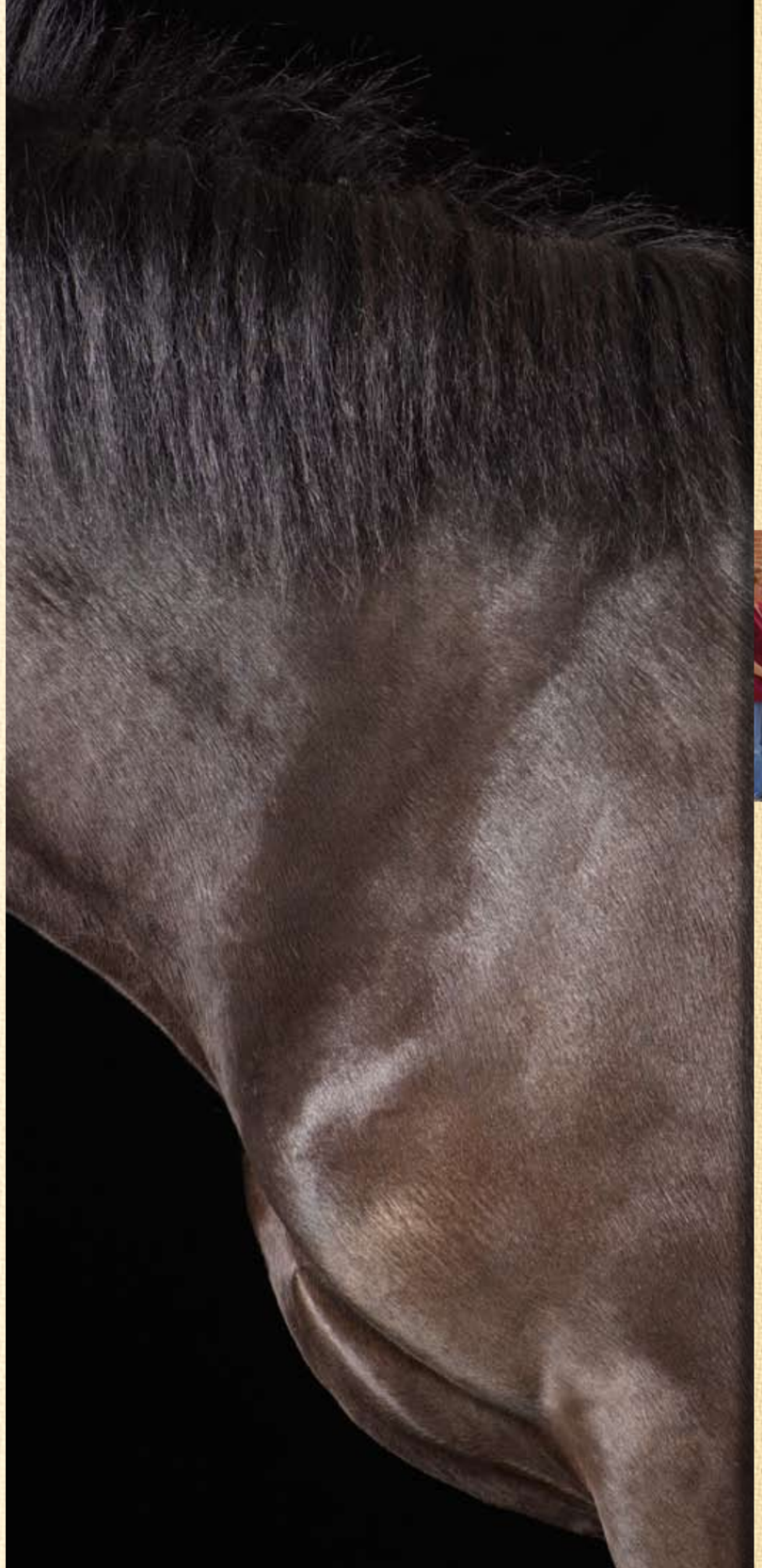

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GUIDE TO
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FOREWORD BY DR. NICHOLAS FRANK

This guide has been written to provide equine practitioners with current information about insulin resistance and laminitis in horses. The authors discuss these complex conditions and provide management and treatment recommendations. LLOYD, Incorporated, (Shenandoah, Iowa), the manufacturer of Thyro-L®, financed this project, but the authors were entirely responsible for the content of this guide.

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CHAPTER 1

Introduction and Definitions

Dr. Nicholas Frank

This guide focuses upon ***insulin resistance*** (IR), which is functionally defined as a reduction in the ability of insulin to stimulate tissues. There are some physiological causes of IR, including pregnancy and stress, but we are concerned with chronic IR and acute exacerbations of this condition. It is important to diagnose and manage IR because insulin-resistant horses, ponies, and donkeys are more susceptible to ***laminitis***.[1]

Pituitary pars intermedia dysfunction

Pituitary pars intermedia dysfunction (PPID) will be discussed first because this is a common endocrine disorder of older horses and is accompanied by IR in some, but not all, cases. Other names for PPID include equine Cushing's disease, pituitary Cushing's disease, or pituitary-dependent hyperadrenocorticism. Older (more than 20 years) horses are more commonly affected, but it is likely that pituitary dysfunction develops in middle-aged animals (10 to 20 years) before obvious clinical signs are seen. The age at which PPID develops varies between individual animals and may be genetically determined. This disorder is more difficult to recognize in its earlier stages, so we will use the terms ***early PPID*** and ***advanced PPID*** to describe affected horses. Some horses with PPID suffer from concurrent IR, whereas others have normal insulin sensitivity **(Figure 1.1)**. *It is therefore necessary to test for both disorders in order to determine whether the patient suffers from PPID, chronic insulin resistance, or both problems concurrently.*

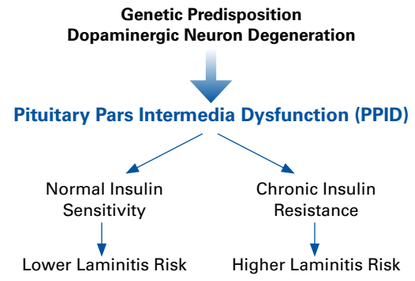

Figure 1.1 Relationship between pituitary pars intermedia dysfunction (PPID) and insulin resistance in horses

Equine metabolic syndrome

We currently use the term ***equine metabolic syndrome*** (EMS) to describe any horse or pony with chronic IR that does not suffer from PPID. However, this only refers to detectable PPID, which may not represent the full spectrum of pituitary dysfunction in horses.

An EMS phenotype is taking shape and components of this syndrome now include obesity, regional adiposity, IR, increased laminitis risk, hypertriglyceridemia, hyperleptinemia, and hypertension.[1-3] It is useful to group these problems together as a syndrome because horse owners and veterinarians are then prompted to evaluate the whole animal when laminitis is detected.

Equine metabolic syndrome occurs more commonly in obese horses and ponies, but is also seen in leaner animals. When obesity develops, it is often the result of an interaction between genetics and environment. Horses or ponies that are metabolically efficient become obese when fed more calories than needed and exercise is minimal. Insulin resistance develops as a consequence of obesity in horses, but it is important to note that not all obese horses are insulin resistant (**Figure 1.2**).

Our current understanding of chronic IR in the lean horse is very limited, but several explanations have been proposed. One explanation is that the liver responds differently to nutrients in affected animals. Ponies studied by a research group at the Royal Veterinary College in the United Kingdom showed exaggerated insulin responses to a meal containing fructose, which suggests that these animals were more affected by this nutrient.[4] It is possible that the liver responds differently to nutrients in lean horses and ponies with EMS, and this leads to a condition of ***hepatic insulin resistance***.

Another proposed cause of IR in leaner animals is the production of cortisol within adipose tissues surrounding the abdominal organs. This visceral fat may be more abundant or active, even in the leaner animal. Local cortisol production may affect the liver and induce hepatic IR through this mechanism. This is referred to as ***peripheral Cushing's disease***, but is not related to PPID.[5]

Finally, horses may suffer pancreatic disease, including insulinomas, pancreatic exhaustion, or pancreatitis. Horses and ponies with exceptionally high blood insulin levels are sometimes encountered. This suggests the presence of an insulinoma, although this tumor has not been documented in the horse. Growth hormone-secreting tumors could also induce marked IR, but this disease has not been reported. Type 2 diabetes mellitus has been detected in a small number of horses with hyperglycemia and glucosuria,[6,7] and pancreatic exhaustion is likely in these cases. Pancreatitis has also been reported in horses and may occur more frequently than previously thought.[8,9] Evidence of pancreatic disease is sometimes detected upon post mortem examination.

Transition state

Some horses with EMS subsequently develop PPID and a ***transition state*** can be recognized. This transition state is more apparent in obese horses with EMS because they undergo a recognizable shift in energy metabolism. The affected horse transitions from being an easy keeper to requiring more calories for weight maintenance. Obese horses lose weight over time as pituitary dysfunction progresses and skeletal muscle mass decreases. Delayed shedding of the winter haircoat may be noted at this time. It is important to note that IR persists in many of these animals even after they become leaner, so the horse remains at higher risk for laminitis. We have recognized a progression of endocrine disorders over time, as depicted in **Figure 1.3**. The obese horse with EMS transitions into a leaner body condition as PPID develops and pituitary dysfunction replaces obesity as the cause of IR.

It is interesting to speculate that this transition explains why horses are more likely to develop laminitis when they become middle-aged. A horse with EMS is already susceptible to laminitis, but this susceptibility is accentuated when pituitary dysfunction develops. This layering of one problem on top of another may significantly increase the risk of laminitis.

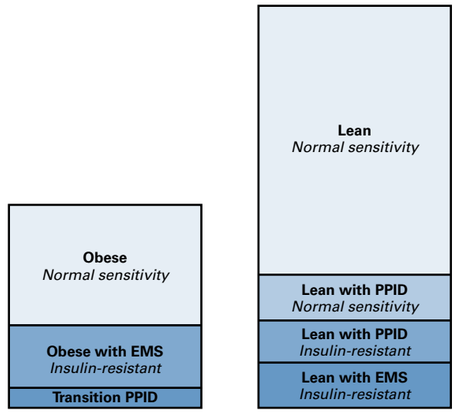

Figure 1.2 Hypothetical distribution of endocrine disorders

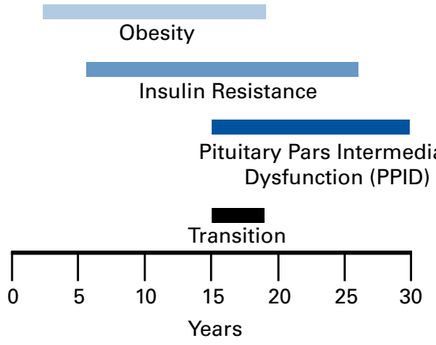

Figure 1.3 Observed time course of endocrine disorders in some patients

If this discussion has left you confused, we can take a simpler approach and examine two case examples.

Case example 1: Equine metabolic syndrome

The first horse is a five-year-old Quarter Horse gelding that is being examined in early May for the problem of laminitis. This episode of laminitis began a few weeks after the pasture grass turned green after the winter. The horse is obviously obese, has a thick neck crest (cresty neck), and there is fat accumulation within the prepuce. Upon further questioning, the owner reports that the horse has been fed five pounds sweet feed morning and evening throughout the winter and has not been ridden in the past two months. This is a case of equine metabolic syndrome because problems are occurring in a young horse that is very unlikely to suffer from PPID. The obesity-associated IR detected in this patient will prove to be reversible with good diet and management practices. After changing the diet and instituting an exercise program, this horse will lose weight, return to normal insulin sensitivity, and the susceptibility to laminitis will decrease. A genetic predisposition towards obesity will remain, but further problems can be prevented by appropriately managing the patient.

Case example 2: Pituitary pars intermedia dysfunction

The second horse is a 28-year-old Thoroughbred mare that is also being examined for the problem of laminitis. Her owner reports that the mare lost weight recently and was slow to shed her winter haircoat last spring and summer. The mare suffers from hirsutism and has a pot-bellied appearance. She is generally thin, but has a cresty neck and fat pads close to the tailhead. This mare suffers from advanced pituitary pars intermedia dysfunction (PPID; also called equine Cushing's disease) and will require medical treatment in the form of pergolide

given orally every day for the rest of her life. However, IR occurs in some, but not all, of these cases, so testing should be performed and diet and exercise changes may be necessary. Laminitis can be prevented by taking two approaches with these patients—treating PPID medically by administering pergolide and managing IR if it is occurring. This two-pronged approach will markedly lower the risk of further laminitis episodes.

In both cases, the key question is whether IR is present and contributing to the development of laminitis. Insulin resistance lowers the threshold for laminitis in horses and it makes it more likely for the affected animal to develop laminitis in response to changes in pasture grass carbohydrate composition or intestinal disease (**Figure 1.4**). As we will explain in this guide, IR can only be diagnosed by testing the animal under appropriate conditions. This guide provides the practitioner with recommendations for testing, current information about IR in horses, and advice on the management and treatment of EMS and PPID.

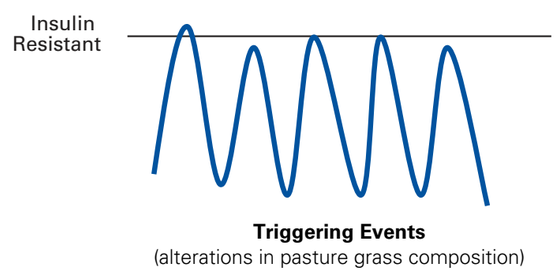

Figure 1.4 Threshold concept for insulin resistance. The laminitis threshold is lowered as insulin sensitivity decreases, which makes it more likely for disease to develop in response to changes in pasture grass abundance and/or carbohydrate composition.

Finally, ***pasture-associated laminitis*** must be defined because IR is an important predisposing factor for this condition.[1] Insulin resistance is exacerbated by changes in the nutrient composition of the grass and the total amount of forage available for consumption. Increased sugar intake exacerbates IR in susceptible animals and may also trigger laminitis by inducing intestinal disturbances. This can result in the movement of endotoxins, exotoxins, or other bacterial by-products into circulation.[10,11] These circulating factors alter endothelial cell function and may affect blood flow within the hoof, which can lead to the stimulation of matrix metalloproteases and separation of the laminae at the dermo-epidermal junction.[12-14]

Insulin resistance may predispose the animal to laminitis through a number of different pathways, including loss of insulin-mediated vasodilation.[15,16] It is also possible that acute exacerbations in IR directly induce laminitis in susceptible animals. Laminitis has been experimentally induced in healthy ponies by infusing insulin and glucose intravenously.[17]

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CHAPTER 2

Establishing an Endocrine Monitoring Program

Dr. Nicholas Frank

Endocrine testing should be included in routine healthcare programs for all horses to identify animals that are at higher risk for developing ***laminitis***. An endocrine monitoring program can be instituted for affected animals and should include assessment of the patient as well as management practices such as feeding regimens, exercise schedules, and pasture turnout.

Three steps should be followed to establish a program in your practice:

Step 1:
Identify a laboratory that measures hormones in equine blood samples

It is very important to identify a laboratory that accepts equine blood and uses assays that have been validated for the horse. The laboratory must be able to process samples efficiently and provide results quickly. Hormone assays sometimes vary between laboratories and results may be reported in different units. Consistency is important, so it is sometimes necessary to assess the performance of the laboratory yourself. Periodically send two tubes of blood from the same horse and compare the results. If the laboratory is providing consistent results, values from the same horse should vary by less than ten percent.

Two examples of laboratories that measure hormones in equine plasma are:

Cornell University College of Veterinary Medicine Animal Health Diagnostic Center (www.diaglab.vet.cornell.edu); ph (607) 253-3900

Michigan State University Diagnostic Center for Population and Animal Health (www.animalhealth.msu.edu); ph (517) 353-1683

Step 2:
Explain the importance of endocrine testing to your clients

Client education seminars or information sheets can be prepared to explain the importance of endocrine testing to your clients. This is a preventative medicine program and should be discussed in the same way as vaccinations and deworming. Laminitis is a major disease, so this is the focus of the program. Horses with ***pituitary pars intermedia dysfunction*** (PPID; ***equine Cushing's disease***) also suffer from immunosuppression that can lead to medical problems such as tooth root infections, bacterial sinusitis, and sole abscesses.

Step 3:

Institute the program and create a schedule

There are two approaches to enrolling patients in an endocrine monitoring program. The first approach is based upon need, so only horses that have suffered from laminitis are included. Alternatively, all obese, geriatric, and genetically susceptible horses can be enrolled with the aim of preventing laminitis and other endocrine-related problems. At-risk horses can be identified by their signalment, physical appearance, and environment. For example, obese horses and offspring of horses with laminitis are at higher risk for ***equine metabolic syndrome*** (EMS) and horses older than 20 years of age should be included because they are more likely to suffer from PPID.

Once the horse has been enrolled in the program, evaluations should be performed every six months when other routine procedures such as vaccinations are scheduled. The evaluation sheet used at the University of Tennessee is included as **Appendix 1** and the form used to record physical measurements is provided as **Appendix 2**. Appointments should be scheduled in advance and reminders sent. The fee charged for an endocrine evaluation should reflect the time spent examining the horse and assessing the history. Endocrine testing should be performed in the morning before 10:00 AM, and it is important to collect blood samples before any horses in the barn are stressed by other procedures such as vaccination or dental examinations. Horses must be kept off pasture and no grain should be fed for 12 hours before testing. It is generally better to withhold all feed for six hours before blood samples are collected for insulin measurements, but some horses must be fed hay to prevent them from becoming agitated. If the horse will tolerate a short period of feed deprivation, instruct the owner to leave one flake of hay in the stall after 10:00 PM the night before and do not provide any feed the morning of testing. It may be better to withhold feed from all horses in the barn on the morning of testing because some animals become stressed when they hear or see others being fed.

In one respect, endocrine testing is easier to perform if the horse is brought to a facility and kept overnight. However, this advantage may be offset by the negative impact of stress on endocrine test results. Some horses will be stressed when they are brought to an unfamiliar environment, so they should be given several days to acclimate to their new surroundings before testing is performed.

CHAPTER 3

Pituitary Pars Intermedia Dysfunction

Dr. Nicholas Frank

Pituitary pars intermedia dysfunction (PPID) affects older horses and is also known as ***equine Cushing's disease*** (ECD). Both terms refer to the same disorder, which is a form of pituitary-dependent hyperadrenocorticism. However, it is preferable to use the term PPID because pituitary dysfunction develops before classical signs of hyperadrenocorticism are recognized.

PPID and insulin resistance

Insulin resistance is detected in some, but not all, horses with PPID. We assume that IR develops because cortisol antagonizes the action of insulin at the tissue level, but this may be a pre-existing condition in some animals. Cortisol is a stress hormone that inhibits the uptake of glucose into storage sites when energy is needed for glucose-dependent tissues such as the brain. Hyperadrenocorticism may also induce IR by altering the structure and function of insulin-sensitive adipose and skeletal muscle tissues through activation or suppression of gene expression. It was recently found that type 2 glycolytic fast-twitch muscle fibers undergo atrophy in response to PPID, which reduces the functional mass of insulin-sensitive tissue within the body.[1]

We must take a good history when examining horses with PPID because some owners report that their horse previously suffered from ***equine metabolic syndrome*** (EMS). In these situations, IR may be the result of this pre-existing problem or PPID, and it is even possible that both conditions combine to exacerbate the problem. The response to pergolide treatment varies accordingly, with some horses returning to normal insulin sensitivity after treatment, whereas others remain insulin resistant. These persistently insulin resistant patients require more intensive dietary management and may benefit from other medical therapies.

Early versus advanced PPID

Most of us associate PPID with the development of a pituitary tumor, and this is certainly the case with advanced disease. Horses with ***advanced PPID*** are easily recognized by their thinner body condition and long haircoat (hirsutism). However, ***early PPID*** is much more difficult to recognize because pituitary dysfunction first manifests as altered seasonal responses and variation in the amounts and types of hormones produced by the pars intermedia.

Older horses and ponies are at greater risk for developing PPID, so close attention should be paid these animals. Our general recommendation is to begin scheduling biannual wellness examinations for horses or ponies when they reach 20 years of age. However, pituitary dysfunction can also affect middle-aged (10 to 20 years) horses, particularly when they suffer from EMS. These obese insulin-resistant horses should be monitored more closely because we have observed that PPID develops at an earlier age in these animals. It is interesting to speculate that chronic obesity creates a pro-inflammatory/pro-oxidative state that accelerates the degeneration of dopaminergic neurons.

Manifestations of early PPID

- **Delayed haircoat shedding:** Pituitary dysfunction may be first recognized by retention of winter haircoat hair for a few weeks longer than other horses within the same barn. Patchy hair retention is a good indicator. The palmar or plantar aspects of the lower legs should be examined because this is one of the first sites of hair retention. In other horses, hair is retained in patches anywhere across the body, and these hairs may be lighter in color because they have bleached over time.

- **Shift in metabolism:** This guideline arises from our observations of obese insulin-resistant horses that eventually develop PPID. Many of these horses have undergone a shift in metabolism accompanied by the onset of delayed shedding. These horses and ponies have a history of obesity and then lose body condition in the absence of any changes in diet or management. They transition from being easy keepers with respect to their caloric needs to requiring more calories for weight maintenance. This finding emphasizes the importance of routine body condition scoring as a component of biannual wellness examinations.

- **Regional adiposity:** Adipose tissues expand within the neck, which leads to the development of a cresty neck. This may be accompanied by the appearance of fat pads in the rump area, adipose tissue accumulation within the prepuce or mammary gland region, and bulging supraorbital fat pads. This is collectively referred to as regional adiposity or fat redistribution, and these are clinical signs of both EMS and PPID. Our guidelines for interpreting these findings are as follows:
  - *Detection of regional adiposity in a younger (less than 10 years of age) horse should prompt testing for IR. We must be concerned about EMS (laminitis in association with obesity and IR) and treatment will focus upon improving the diet and increasing exercise.*
  - *Detection of regional adiposity in a middle-aged or older horse should prompt testing for both IR and PPID. Treatment will include pergolide therapy if PPID is confirmed, plus management of IR through diet and exercise. If IR persists after management changes have been stringently followed, levothyroxine sodium can be administered to reduce body weight and improve insulin sensitivity or metformin can be considered in leaner, persistently insulin-resistant animals.*

- **Fertility problems:** This is a poorly defined area of our knowledge, but it is likely PPID plays a role in some fertility problems affecting mares, and these issues may arise before the disorder can be readily diagnosed. Unfortunately, fertility problems are often multifactorial, so it is difficult to determine the relative importance of PPID.

Manifestations of advanced PPID

- **Hirsutism:** This clinical sign is pathognomonic for PPID in older horses, and has been used as the gold standard for diagnosing the disease. Early evidence of hirsutism includes retention of the winter haircoat for longer than expected or detection of longer hairs on the palmar or plantar aspects of the lower leg. Hairs are arrested in telogen and may become lighter in color over time. Hirsutism is attributed to alterations in melanocyte-stimulating hormone (MSH) secretion or increased production of androgens by the adrenal cortex.

- **Laminitis:** Horses with PPID are more susceptible to insidious-onset laminitis. Hyperadrenocorticism promotes vasoconstriction and protein depletion within the dermis and epidermis, which may lower the threshold for laminitis.[2] Horses or ponies with PPID are more predisposed to pasture-associated laminitis. This predisposition may be a result of IR, so it is very important to diagnose and manage this problem when managing patients with PPID.

- **Changes in body composition:** Skeletal muscle mass decreases as PPID develops and is often accompanied by regional adiposity. Type 2A (oxidative-glycolytic) and 2B (glycolytic) muscle fibers undergo atrophy.[1] Regional adiposity is characterized by expansion of adipose tissues in specific regions, including the neck, either side of the tailhead, and prepuce. Cortisol-induced protein catabolism results in a thinner body condition, loss of epaxial muscle mass, and rounding of the abdomen.

- **Polyuria/polydipsia:** Owners sometimes report excessive urination and water consumption. Polyuria can be attributed to cortisol-mediated antagonism of anti-diuretic hormone (ADH) in the collecting tubules or glucosuria, which occurs when IR leads to hyperglycemia. Other explanations for polyuria/polydipsia include suppression of ADH secretion by the pars nervosa as a result of compression by neoplastic tissue.

- **Chronic infections and delayed wound healing:** Common examples of this problem include tooth root infections, sinusitis, and sole abscesses. Wounds and lacerations may take longer to heal. These problems are attributed to immunosuppression secondary to hyperadrenocorticism, but tissues may also be weakened by protein depletion.

- **Lethargy:** This problem has been attributed to increased beta endorphin release from the pars intermedia. Horses with advanced PPID also appear to be more tolerant of pain.

- **Hyperhidrosis:** Excessive sweating may simply be a result of hirsutism, but some horses continue to exhibit this problem, even after body clipping. A disturbance in hypothalamic body temperature regulation is suspected in these cases.

- **Central nervous system deficits:** Neurological deficits including seizures are often attributed to pituitary adenomas, but this is a rare occurrence. Optic chiasm lesions would be more likely to occur in these cases, so this finding raises the likelihood of PPID being the cause of neurological disease.

- **Inappropriate mammary gland development and lactation:** This problem is seen in mares with early or advanced PPID and is attributed to increased prolactin secretion from the pars intermedia.

Pathophysiology

Pituitary pars intermedia dysfunction is a progressive endocrine disorder, so terms like early PPID and advanced PPID actually refer to different points along the same continuum. A horse with early PPID is primarily affected by pars intermedia hyperplasia and hypertrophy, whereas signs of advanced PPID are attributed to neoplasia. However, a small pituitary adenoma(s) may be developing in the animal with early PPID and this tumor will enlarge and become more active over time. It has also been proposed that hyperplasia within the pars intermedia is dynamic, even in healthy horses. Hyperplasia is more pronounced in the fall season when the pars intermedia becomes more active, and then regresses during the winter. It is even conceivable that the earliest form of PPID is a change in this seasonal pattern of hyperplasia and regression.

The development of PPID has been tied to the degeneration of dopaminergic neurons over time in susceptible animals.[3] This change occurs through oxidative damage and perhaps inflammation, but individual horses differ in susceptibility, which means that the rate of degeneration varies between animals. This is similar to the loss of dopaminergic neurons seen in humans that suffer from Parkinson's disease, and individual susceptibility plays an important role in the pathophysiology of this condition. Other individual factors such as chronic obesity and IR may advance the development of PPID in horses.

Loss of dopaminergic neurons causes a decrease in dopamine secretion and therefore, a reduction in inhibition. The pars intermedia is under tonic inhibition, which means that activity increases when dopamine levels decline. Loss of dopaminergic inhibition permits cell proliferation and expansion, which increases hormone secretion. This becomes a permissive environment for neoplasia, which develops over time. Hyperplasia and neoplasia are detected upon histopathological examination of tissues from affected animals, but alterations in structure can also occur with age and season. This sometimes makes it difficult to diagnose PPID on the basis of histopathology results alone.

Advanced PPID is caused by the presence of a small tumor(s) within the pars intermedia of the pituitary gland. This tumor is active and produces hormones and other peptides with hormone-like activity. In humans, we refer to the anterior and posterior lobes of the pituitary gland, but these terms are not appropriate for the horse. The equine pituitary gland is arranged differently, with the "anterior pituitary gland" wrapped around the "posterior pituitary gland". It is therefore more appropriate to refer to the anterior pituitary gland as the pars distalis and the posterior pituitary as the pars nervosa. The pars intermedia is located between these two structures.

The pars distalis secretes six hormones: ACTH (also called corticotropin), thyroid-stimulating hormone (TSH; also called thyrotropin), growth hormone (also called somatotropin), follicle-stimulating hormone, luteinizing hormone, and prolactin. In the healthy animal, the pars intermedia is primarily composed of melanotropes that secrete alpha melanocyte-stimulating hormone (α-MSH). Oxytocin and anti-diuretic hormone (ADH; also called vasopressin) are secreted by the pars nervosa.

In the healthy state, the hypothalamic-pituitary-adrenal axis begins with the production of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates corticotropes within the pars distalis of the pituitary gland to produce the prohormone pro-opiomelanocortin (POMC). This large peptide is cleaved by prohormone convertase I to generate ACTH, which enters the circulation and stimulates cortisol release from the adrenal cortex. Circulating cortisol negatively feeds back on both the hypothalamus and pars distalis.

Hormone production within the pars intermedia also begins with POMC, but two enzymes are active within this region of the pituitary gland. Prohormone convertase I cleaves ACTH from POMC and prohormone convertase II converts ACTH into α-MSH. Under normal circumstances, only α-MSH is secreted from the pars intermedia.

Loss of dopaminergic inhibition permits excessive POMC production by the pars intermedia, which increases the secretion of α-MSH and ACTH. Production of ACTH by the pars intermedia is not controlled by negative feedback, so hyperadrenocorticism develops over time. Other products that originate from

POMC pathway are also produced in greater quantities, including beta endorphin, corticotropin-like intermediate peptide (CLIP), other melanocyte stimulating hormones, and β-lipotrophin.

Screening tests for early PPID

- **Clinical judgment**: None of the screening tests listed below are very good at detecting early PPID. It must be assumed that pituitary hyperplasia develops before available tests are able to detect disease, which means that the animal may be at greater risk for laminitis during this period. The first manifestation of PPID is likely to be altered hormonal responses to season that may contribute to the increased risk of laminitis at certain times of the year. Unfortunately, these seasonal alterations may not be detected until clinical signs of delayed shedding develop.

  Practitioners are therefore advised to rely heavily upon their clinical judgment when assessing horses for endocrine disorders. Consider the age and genetic background of the horse and the history provided by the owner. In the author's opinion, veterinarians should trust their clinical judgment over test results unless an extensive range of tests is performed in the patient.

Screening tests for advanced PPID

- **Hirsutism:** Detection of hirsutism in an older horse is sufficient for diagnosis, particularly when accompanied by other clinical signs. No other testing is required. A photograph of a horse with hirsutism is presented as **Figure 3.1**.

- **Complete blood count (CBC):** Hyperadrenocorticism is associated with mature neutrophilia, lymphopenia, and monocytosis. The same response can be seen in a horse that has been stressed prior to blood collection, but in the case of PPID, these alterations persist after stress has subsided.

- **Resting ACTH concentration:** Several commercial laboratories measure plasma ACTH concentrations and may soon offer alpha melanocyte-stimulating hormone (a-MSH) measurements. Care must be taken to collect blood samples under the proper sampling conditions when this test is used. Blood should be collected in the morning after the horse has been kept calm overnight. It is important to recognize that stressful or painful conditions (i.e., during acute laminitis) will raise ACTH levels and may lead to false positive results. Blood should be collected into a plastic tube containing ethylenediamine tetraacetic acid (EDTA). Samples should be refrigerated or kept on ice packs until centrifuged, and centrifugation should be performed within two hours of blood collection. Harvested plasma should be mailed out via overnight shipping the same day or frozen. Samples must be shipped in a cooler with several ice packs.

Pituitary pars intermedia dysfunction is suspected if the plasma ACTH concentration exceeds 35 pg/mL (7.7 pmol/L) and confirmed if the level is above 45 pg/mL (10 pmol/L).

Test results must be interpreted with caution if testing is performed during the autumn months (middle and eastern United States). Plasma ACTH concentrations normally rise during this season, which leads to more false positive results. A negative result is still significant during this season, but horses that that are positive should be retested between January and August.

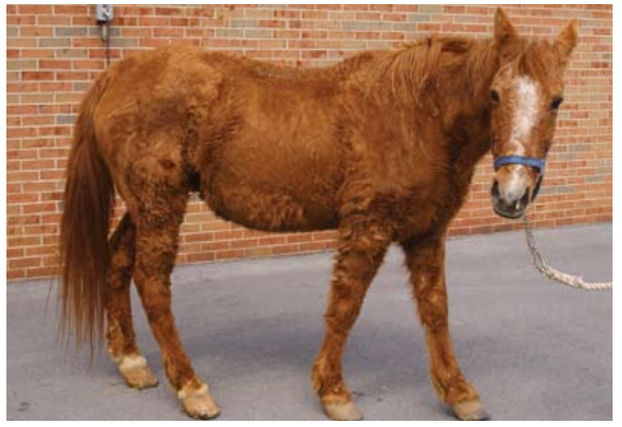

Figure 3.1 A horse with advanced hirsutism attributed to pituitary pars intermedia dysfunction (PPID)

- **Detection of insulin resistance (IR):** As previously discussed, horses can suffer from IR, PPID, or both conditions concurrently. Young or old horses, with or without PPID, can suffer from IR, so insulin sensitivity tests cannot be used to diagnose pituitary dysfunction. However, it is very important to diagnose and manage IR if this condition is present, so testing for this problem is still recommended.

- **Resting cortisol concentration:** Plasma or serum cortisol concentrations vary markedly from minute to minute, so single cortisol measurements *cannot* be used to diagnose PPID.

Diagnostic tests for PPID

Recommended tests

- **Oral domperidone test (ODT):** This test was recently developed by researchers at Purdue University and may be better for detecting early PPID than either resting ACTH concentrations or the dexamethasone suppression test (DST). An information sheet describing the procedure used is included as **Appendix 3**. Briefly, this test involves the measurement of plasma ACTH concentrations before and four hours after oral administration of domperidone. If testing is

performed in the fall, the second blood sample should be collected two hours post-domperidone because the response is magnified during this season. A greater than twofold rise in plasma ACTH concentration over two to four hours indicates that the horse suffers from PPID.

- **Overnight dexamethasone suppression test (DST):** This test is performed by collecting a pre-injection blood sample, injecting dexamethasone intravenously (or intramuscularly) at a dosage of 40 µg/kg body weight (20 mg for a 500-kg horse), and collecting a second blood sample 19 or 24 hours later. In the healthy horse, dexamethasone acts via negative feedback to lower plasma cortisol concentrations for more than 24 hours.

  This test is positive if the plasma cortisol concentration is above 10 ng/mL (equivalent to 1.0 ug/dL or 27 nmol/L) after 19 or 24 hours.

  More false positive DST results occur in the autumn, so it is better to test horses between January and August. If testing is performed in the fall, only the negative test result is significant. Horses that test positive in the autumn must be retested during a different season.

  Many horse owners will be concerned about the possibility of laminitis developing after dexamethasone injection. The risk of laminitis following dexamethasone injection has never been quantified, but is very low in our experience. However, horses and ponies with IR may be a greater risk, so this test should be used with caution in animals with obesity, regional adiposity, or IR.

- **Intravenous thyrotropin-releasing hormone (TRH) test:** This test was first developed by Beech and Garcia in 1985[4] and originally focused upon the blood cortisol response. However, it has recently been established that plasma ACTH concentrations rise following TRH administration, and this is a better measure of the response.[5] Horses with PPID exhibit a more pronounced increase in ACTH concentrations after TRH. Unfortunately, injectable TRH is not commercially available, so it must be prepared in a laboratory and the purity of the product cannot be guaranteed. As a result, this test is primarily used for research purposes. Practitioners may choose to purchase and prepare reagent-grade TRH for injection, but this product should only be administered after an informed consent form has been signed by the owner.

- **Combined dexamethasone suppression/TRH stimulation test:** This combined test is more accurate because it includes two components and is positive for PPID if an abnormal response is detected with either component. The DST is the same as described above, but TRH is also injected three hours after dexamethasone. A pre-injection blood sample is collected, followed by injection of dexamethasone as described above. Three hours later, another baseline blood sample is collected and then TRH (1.0 mg total) is injected intravenously, followed by a second blood sample collected 30 minutes later. The TRH component of the test is positive if the plasma cortisol concentration is greater than 66 percent higher when measured 30 minutes after TRH administration. The lack of a commercially available injectable form of TRH also limits the use of this combined test.

Other tests

- **Diurnal cortisol rhythm test**: Plasma cortisol concentrations generally decrease throughout the day, so a diurnal cortisol rhythm test has been developed to detect PPID. This test is performed by collecting a blood sample in the morning and then again in the evening. The test is positive if the cortisol concentration does not decrease by 30 percent throughout the day. However, this test is not recommended because our research group has detected a high number of false positive results when this test is performed. False positive results are often caused by stress and it has been shown that moving horses from pasture into stalls disrupts the cortisol rhythm.[6] If the test is used, you should *only consider the negative result to be significant*. Horses with positive results must be evaluated with a more specific test before the diagnosis of PPID is made.

- **ACTH stimulation test:** This test is only used if an adrenal tumor is suspected and results are difficult to interpret because some horses develop adrenal hyperplasia secondary to PPID. Adrenal tumors should be suspected when clinical signs of advanced hyperadrenocorticism are present in the absence of hirsutism.

Treatment

There are three approaches to managing patients with PPID: 1) control of the disorder through drug therapy, 2) avoidance of laminitis through careful management practices, and 3) diagnosis and management of IR if this problem is present.

Drug therapy

Three drugs can be used to treat PPID in horses, but pergolide is the treatment of choice at this time. Once treatment has been initiated, patients must be treated for the rest of their lives, so this financial issue should be discussed. Horse owners should also consider the consequences of withholding treatment, including an increased risk of laminitis and expenses associated with veterinary care and corrective shoeing.

- **Pergolide mesylate:** This is a dopaminergic agonist that inhibits the activity of the pars intermedia and may slow the progression of PPID. Dopamine suppresses the activity of the pars intermedia and therefore ACTH production. This drug is widely used and is the most effective treatment for PPID. Pergolide was available in a tablet form (Permax®) that was used for the treatment of Parkinson's disease. However, the Food and Drug Administration withdrew approval for pergolide use in humans when it was discovered that long-term pergolide administration increased the risk of valvular regurgitation.[7,8] In addition to its other properties, pergolide acts through 5-HT_{2B} receptors within the heart to cause thickening

of the mitral, aortic, and tricuspid valves. However, the dosages used in humans (3 mg/day on average for five years) were much higher than those used in horses if body weight is taken into account. The risk to horses is likely to be very low, but cardiac auscultation should be performed every six months in treated patients. Heart murmurs are often detected in older patients, but these problems should be monitored in horses that are being treated with pergolide.

A starting dosage of 1 mg pergolide (total dose) orally (or 0.002 mg/kg body weight) divided twice daily is recommended. Responses to therapy include increased physical activity, decreased recurrence of laminitis, improved insulin sensitivity, gain in muscle mass, return to normal shedding pattern, and improvement in polyuria/polydipsia.

Diagnostic tests can be repeated after 30 days of treatment to assess responses to therapy. Resting ACTH concentrations are often measured for this purpose, but this approach is not always reliable. Some horses normalize with respect to ACTH levels, but do not improve clinically. Other patients show an excellent clinical response, but plasma ACTH concentrations remain elevated. This highlights the importance of clinical judgment in the management of PPID. The dosage of pergolide should be increased by 0.5 or 1.0 mg/day if clinical signs have not improved after 30 to 90 days. The maximum dosage of pergolide used in our practice is 5 mg/day. Anorexia may be observed in some horses when treatment is initiated. If this happens, the horse should be taken off pergolide for a few days and then started back on the drug at a lower dosage. The dosage should be raised gradually in these patients.

One response to pergolide treatment is the normalization of glucose-insulin metabolism in PPID patients with concurrent IR. This has become an important part of our management plan for PPID and is discussed below.

- **Trilostane:** This drug is used in Europe, but cannot be purchased in the United States. However, it can be imported from Canada with special approval. Trilostane acts at the adrenal cortex by inhibiting the enzyme 3-β-hydroxysteroid dehydrogenase, which is involved in cortisol production. This drug is available in 30, 60, or 120 mg capsules (Vetoryl®, Arnolds Veterinary Products Ltd, UK) and is given orally in the afternoon or evening at a dosage of 0.75 or 1.0 mg/kg body weight once daily.

- **Cyproheptadine:** Many horses and ponies were treated with cyproheptadine before pergolide became the treatment of choice. Cyproheptadine inhibits the action of the excitatory neurotransmitter serotonin and therefore reduces the activity of the pars intermedia. Dosages range from 0.25 mg/kg once daily to 0.5 mg/kg twice daily, and depression is seen in some animals when treatment is initiated. Individual horses and ponies vary markedly in their response to cyproheptadine, so treatment failures are more common with this drug. The response to pergolide is more consistent, so this drug has largely replaced cyproheptadine. Pergolide and cyproheptadine are occasionally used in combination, and may provide a better response.

Avoiding laminitis

Laminitis is a major concern for any horses with PPID, so every effort should be made to lower the risk of disease. It is important to treat the underlying problem of PPID because hyperadrenocorticism may be weakening hoof structures and making them more susceptible to damage. Treatment of PPID also addresses the problem of IR if this condition is being induced by hyperadrenocorticism. Insulin resistance is further increasing the risk of laminitis, so it is very important to manage this problem. If pergolide therapy alone does not return the horse to normal insulin sensitivity, stricter dietary recommendations must be made. Recommendations should include limiting sugar and starch intake, and controlling access to pasture. Exercise is also recommended to preserve muscle mass and improve insulin sensitivity.

It is often necessary to adjust management practices and this can be the hardest part of the management plan for owners to accept. The most important point to make is that pasture grazing increases the risk of laminitis. Consumption of large amounts of sugars, starches, and proteins on pasture potentially exacerbates IR and leads to the gastrointestinal events that can trigger laminitis. The patient with PPID is more susceptible to laminitis, particularly if it concurrently suffers from IR.

Grazing on pasture must be eliminated completely if the patient currently suffers from laminitis. Turnout can resume on a very limited basis once the feet have stabilized and treatment for PPID has been initiated. This should be limited to less than one hour twice daily at first, and a grazing muzzle is recommended. As the time on pasture is increased, it is better to extend the number of short periods per day, rather than the length of each period. The amount of time spent on pasture should be determined by the degree of IR and history of laminitis. Some horses are extremely sensitive to pasture laminitis and must be denied access to grass at all times. However, most horses can be returned to pasture for limited periods of time if turnout is gradually increased over several weeks and a grazing muzzle is worn. Horse owners should be instructed to monitor growth conditions in their pastures, and to reduce turnout time when the grass is growing quickly.

Diagnosis and management of IR

All horses with PPID should be screened for IR and this is easily accomplished. One commercial laboratory (Cornell University Animal Health Diagnostic Center) measures the resting insulin concentration in the same blood sample collected for ACTH measurements. Other laboratories prefer to work with serum, so another tube of blood must be collected at the same time. This screening test for IR has its limitations, but is very helpful for identifying horses and ponies that suffer from

moderate to severe IR. Simply including this test in your endocrine evaluation will significantly increase the number of cases identified and thereby reduce the likelihood of subsequent laminitis episodes.

The limitations of this screening test are 1) pain and stress associated with laminitis interfere with the test because they raise insulin levels, 2) resting insulin concentrations can be within reference range if only mild/early IR is present, 3) resting insulin concentrations fluctuate over time, and 4) insulin levels sometimes fall back into reference range if pancreatic exhaustion develops after prolonged IR. Glucose concentrations can be measured at the same time and this information helps to identify horses with chronic IR and pancreatic exhaustion. Hyperglycemia and sometimes glucosuria are detected in these animals because insulin is not secreted in sufficient quantities to move glucose into tissues.

Reference ranges vary between laboratories and depend upon the assay used to measure insulin. It is better to use the reference range provided by the laboratory, provided that this range has been established for horses. A radioimmunoassay is used to measure insulin in our laboratory and IR is diagnosed when the insulin concentration exceeds 20 µU/mL (same as mU/L) if the horse has been deprived of feed (fasted) for six hours prior to sampling. When hay is fed before blood collection, IR is suspected when an insulin concentration above 30 µU/mL is detected, but these patients should be retested under fasting conditions. Horses with results that fall below 20 µU/mL should undergo dynamic testing if IR is still suspected. The combined glucose-insulin test (CGIT) is recommended for this purpose. Some laboratories report insulin concentrations in pmol/L and these values can be converted to µU/mL by dividing by seven.

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CHAPTER 4

Diagnosis of Equine Metabolic Syndrome (EMS)

Dr. Nicholas Frank

We currently use the term equine metabolic syndrome (EMS) to describe any horse or pony with chronic IR that does not suffer from PPID. However, this only refers to detectable PPID, which may not encompass the full spectrum of pituitary dysfunction in horses.

An EMS phenotype is emerging as more research is being performed, and components of this syndrome now include obesity, regional adiposity, IR, increased laminitis risk, hypertriglyceridemia, hyperleptinemia, and hypertension.[1-3] It is useful to group these problems together as a syndrome because this prompts horse owners and veterinarians to evaluate the whole animal when laminitis is first detected.

Equine metabolic syndrome occurs more commonly in obese horses and ponies, but is also seen in leaner animals. When obesity develops, it is often the result of an interaction between genetics and environment. Horses or ponies that are metabolically efficient become obese when provided with more calories than required. Insulin resistance develops as a consequence of obesity in horses, but it is important to note that not all obese horses are insulin resistant (**Chapter 1; Figure 2**).

The term ***Metabolic Syndrome*** was first proposed by Johnson[4] in 2002, but the descriptor 'equine' has been added to differentiate this syndrome from the one recognized in humans. Metabolic Syndrome is a set of risk factors for coronary heart disease, stroke, or diabetes in humans, whereas EMS is a clinical syndrome unique to the horse because of its connection with laminitis.

Pre-laminitic metabolic syndrome (PLMS) is a term that has been used by the research group at Virginia Tech University to describe ponies that are more susceptible to pasture-associated laminitis. If one of these animals were examined, it would be appropriate to record the diagnosis as EMS because this term describes the clinical condition.

Obesity and laminitis have been attributed to hypothyroidism in the past because low resting total triiodothyronine (tT_3) and total thyroxine (tT_4) concentrations are sometimes detected in affected horses. However, we now recognize that low resting thyroid hormone concentrations often accompany nonthyroidal illness,[5] so this finding is more likely to be a consequence, rather than a cause of obesity. A diagnosis of hypothyroidism should not be made unless the animal responds inappropriately to hormone challenges. Unfortunately, a thyroid-stimulating hormone (TSH) assay is not available for horses.

Clinical presentation

Laminitis is the presenting complaint in many cases, but physical characteristics of EMS are sometimes recognized by veterinarians during routine healthcare visits.

Metabolism: Observations made by owners often alert the veterinarian to a potential problem. Horse owners sometimes observe that their horse is overweight even after caloric intake has been limited. These animals are described as easy keepers and seem to be more efficient with respect to their energy metabolism.

Genetics: We have observed that certain mares produce offspring that develop EMS when they mature, and this provides some evidence of a genetic influence. Treiber et al.[1] found that laminitis predisposition followed a genetic pattern in an in-bred population of ponies, and it is likely that we will eventually identify defects in genes that determine metabolic efficiency in horses. At present, veterinarians should simply recognize that the offspring of horses affected by EMS are more likely to develop the condition. This does not mean that a mare or stallion with EMS should not be bred, but diet and exercise programs must be established for the offspring.

Breed: In our practice, pony breeds, Morgan horses, and Paso Finos are most commonly affected, but we have detected the problem in Arabian, Quarter Horse, Saddlebred, Missouri Foxtrotter, Tennessee Walking Horse, and Warmblood breeds. Thoroughbreds and Standardbreds are less likely to be affected, but EMS affects all breeds, particularly when overfeeding occurs.[2] When viewed simplistically, easy keeper breeds are most commonly affected, whereas hard keeper breeds are less likely to develop EMS. Breed predispositions are often magnified by overfeeding.

Age: Susceptibility to EMS may be established from birth and obesity develops in some horses as soon as they reach maturity. However, most horses are between 5 and 15 years of age when veterinary or farrier services are first requested because of laminitis. This delay may indicate that horses must suffer from chronic obesity before IR develops or that progressive damage to hoof structures must occur before lameness is detected. It is also possible that laminitis first develops in middle-aged horses when pituitary dysfunction begins to become a problem. This layering of one endocrinopathy on top of another may significantly increase the susceptibility to laminitis. Most horses are out on pasture when

laminitis first develops, and it is likely that this event is triggered by diet-induced exacerbation of IR or intestinal disturbances caused by grazing on sugar-rich grass. Minor subclinical laminitis events may occur before the problem is recognized by the client.

Laminitis: Active laminitis is detected when lameness is observed, but it is likely that some horses have undergone minor subclinical events that escaped detection, particularly when the horse is rarely ridden. Evidence of prior laminitis comes from a history of foot soreness when grazing on pasture or by detection of divergent growth rings on the hooves (founder lines). These growth rings are spaced farther apart at the heels than the toe and are assumed to result from previous subclinical laminitis episodes **(Figure 4.1)**. Some affected horses show radiographic evidence of third phalanx rotation, even when they are sound at the time of examination.

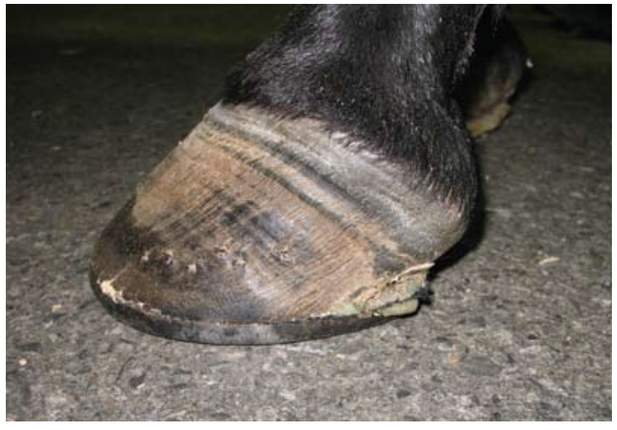


Figure 4.1 Photograph showing divergent hoof rings (founder lines) on the foot of a horse with radiographic evidence of laminitis

Other presenting complaints: Equine metabolic syndrome is sometimes first recognized when horses are presented with colic resulting from a pedunculated lipoma, hyperlipemia, or reproductive problems. We have observed that horses with EMS develop pedunculated lipomas at a younger age, presumably because of additional fat surrounding the abdominal viscera. Obesity has also been asso-ciated with abnormal reproductive cycling in mares.[6]

Geldings are sometimes presented for evaluation of a swollen sheath **(Figure 4.2)** and mares can show enlargement of the mammary glands. Both of these problems are related to adipose tissue accumulation and this interferes with lymphatic return in these regions. Affected horses develop edema when they are left standing in their stall for too long, but this problem improves with exercise.

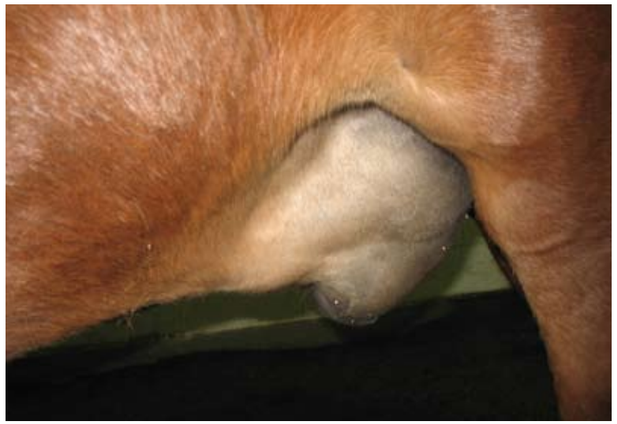


Figure 4.2 Photograph illustrating enlargement of the prepuce in an obese insulin-resistant gelding

Importance of recognizing insulin resistance: In addition to the risk of laminitis, it is also important to recognize EMS before administering intravenous fluids or total parenteral nutrition solutions containing dextrose to patients, because problems with hyperglycemia and glucosuria are more likely to occur. Regular insulin can be administered intravenously as a continuous rate infusion to address this problem, while using a hand-held glucometer to monitor blood glucose concentrations. Hyperglycemia is also encountered when insulin-resistant horses are given partial or total parenteral nutrition, and this can lead to glucosuria, osmotic diuresis, and fluid losses.

Insulin resistance should also be considered before high-sugar feeds are provided to horses with EMS. Complete pelleted feeds are sometimes given to horses after colic surgery or to patients that require tube feeding. These feeds can exacerbate IR and trigger laminitis events in susceptible animals. Lactulose is sometimes administered to patients with liver failure and this treatment has triggered laminitis in the past. This problem was encountered by the author when lactulose was administered to a horse with EMS that suffered from liver failure. Severe laminitis developed within 48 hours and the patient was euthanized a week later, after recovering from liver disease.

Clinical signs

Physical characteristics: Most chronically insulin-resistant horses and ponies exhibit physical characteristics of EMS, which include generalized obesity and/or regional adiposity. Presence of a cresty neck is the most important form of regional adiposity in horses and mean neck circumference has been negatively

correlated with insulin sensitivity in a small group of obese insulin-resistant horses.[2] The neck crest is raised and thicker **(Figure 4.3)**, and may fall over to one side in severely affected ponies and donkeys. A more pronounced neck crest is normal for some breeds of horse and common in stallions, so this normal variation must be accounted for.

Noticeable fat deposits may be found next to the tailhead, within the prepuce or mammary gland region, in the supraorbital fossae **(Figure 4.4)**, and occasionally as randomly distributed subcutaneous masses across the body **(Figure 4.5)**.

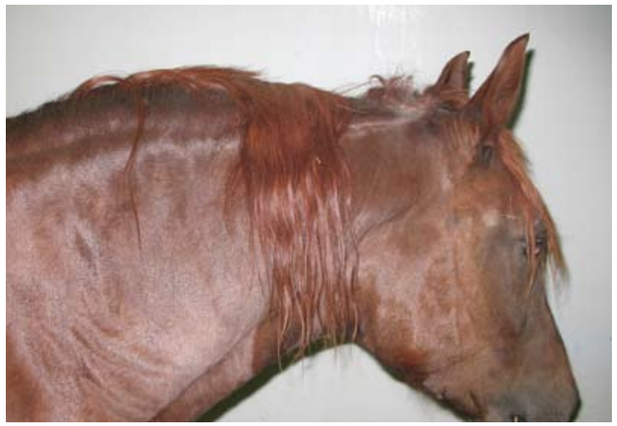


Figure 4.3 Photograph showing the enlarged neck crest of an obese insulin-resistant horse

Figure 4.4 Photograph of a horse with bulging supraorbital fat pads

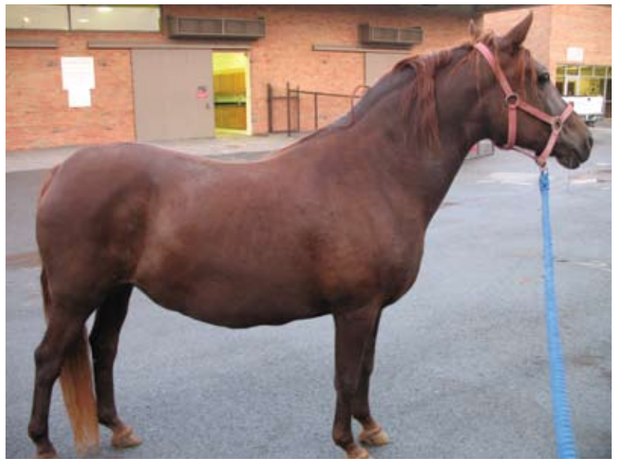


Figure 4.5 Photograph of an obese Morgan horse mare suffering from equine metabolic syndrome with randomly distributed subcutaneous fat pads across the ventral abdomen

Laminitis: As stated above, laminitis signs vary from profound lameness that prevents the horse from walking or standing, to clinically undetectable damage. Evidence of laminitis may only be provided by histopathological examination in some cases, or when radiographs are taken of the feet.

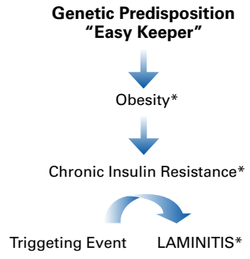
Pathophysiology

Obese horses with EMS

Most of the cases seen in our practice are obese horses or ponies with EMS. This syndrome begins with a genetic predisposition towards obesity that is likely to be determined by metabolic efficiency. These animals are referred to as easy keepers because they require fewer calories to maintain body weight. Many of them also have ravenous appetites and spend more time grazing when turned out on pasture. The easy keeper concept is relevant to the issue of genetic susceptibility. Certain breeds or genetic lines may have undergone evolutionary adaptations to survive in harsher environments, and these horses or ponies may be more efficient at converting poorer quality forages into energy.

Genetics and environment interact in these horses when they are given free access to pasture, particularly when only a few animals are grazing on a large area. In many regions of the country, pasture grass is abundant and rich in nutrients. This is accentuated when certain types of grass are sown to improve pastures for grazing cattle or after the application of fertilizers. A second point of interaction between genetics and environment occurs when obese horses are fed grain.

This is unnecessary for these metabolically efficient animals and promotes obesity and IR. Unfortunately, many horse owners feed grain to entice their horses in from pasture or because they think that the horse is unhappy if it is deprived of this feed. Finally, we interfere with an important interaction between genetics and environment when we feed horses more in the winter to prevent weight loss. Seasonal weight loss is a natural occurrence in wild horses and is likely to correct any problems with obesity that develop during the rest of the year.



*Three components of equine metabolic syndrome (EMS)

Figure 4.6 Flow chart illustrating the presumed progression of events in obese insulin-resistant horses

Overfeeding genetically susceptible horses promotes obesity. It is a common mistake to feed grain to horses that are maintaining acceptable body conditions when grazing on pasture. This can occur when horses with different metabolic needs are fed together or when grain is used as a reward. Some horse owners deliberately feed their horse too much because they prefer higher body condition scores and these biases are reflected in certain breed associations and show classes. Other horse owners simply fail to recognize obesity. Veterinarians should provide advice in this area and warn owners about the dangers of obesity-associated IR and laminitis.

Relationships between obesity and IR are complex. It should be remembered that *not all obese horses are insulin resistant and IR is not always accompanied by obesity*.[1,6] However, these conditions are associated, and there is evidence that IR predisposes ponies to laminitis.[1,7] All of the pieces of the puzzle must be assembled before we can fully understand the association between IR and laminitis in horses and ponies. However, there are three broad mechanisms by which IR and obesity could predispose horses to laminitis: 1) altered blood flow or endothelial cell function within the vessels of the foot, 2) impaired nutrient delivery to hoof tissues, or 3) a pro-inflammatory or pro-oxidative state induced by chronic obesity and IR. The insulin-resistant horse has a lower threshold for laminitis, which means that triggering events that are tolerated by horses with normal insulin sensitivity precipitate laminitis episodes in the animal with IR **(Figure 4.6)**.

Lean horses with EMS

Our current understanding of chronic IR in the lean horse is very limited, but several explanations have been proposed. One explanation is that the liver responds differently to nutrients in affected animals. Ponies studied by a research group at the Royal Veterinary College in the United Kingdom showed exaggerated insulin responses to a meal containing fructose, which suggests that these animals were more affected by this nutrient.[8] It is possible that the liver responds differently to nutrients in lean horses and ponies with EMS, and this leads to a condition of ***hepatic insulin resistance***.

Another proposed cause of IR in leaner animals is the production of cortisol within adipose tissues surrounding the abdominal organs. This visceral fat may be more abundant or active, even in a leaner animal. Local cortisol production may affect the liver and induce hepatic IR through this mechanism. This is referred to as ***peripheral Cushing's disease***, but is not related to PPID.[4]

Finally, horses may suffer pancreatic diseases, including insulinoma, pancreatic exhaustion, or pancreatitis. Horses and ponies with exceptionally high blood insulin levels are sometimes encountered. This suggests the presence of an insulinoma, although this tumor has not been documented in the horse. Growth hormone-secreting tumors could also induce marked IR, but this disease has not been reported. Type 2 diabetes mellitus has been detected in a small number of horses with hyperglycemia and glucosuria,[9,10] and pancreatic exhaustion is likely in these cases. Pancreatitis has also been reported in horses and may occur more frequently than previously thought.[11,12] Evidence of pancreatic disease is sometimes detected upon post mortem examination.

Testing procedures

Two testing procedures are recommended to practitioners—resting glucose and insulin concentrations and the combined glucose-insulin test (CGIT). The first test is easy to perform and should be used to screen every horse with laminitis or physical characteristics consistent with EMS or PPID. This test requires the collection of a single blood sample according to the protocol outlined below. The CGIT is more complicated and is only necessary when EMS is suspected, but cannot be confirmed by measuring resting glucose and insulin concentrations. Horses with mild or early IR fall into this category and this dynamic test is required to confirm the diagnosis in these animals. The CGIT is described below.

It is recommended that practitioners first submit a blood sample to measure resting blood glucose and insulin concentrations. If this test fails to confirm IR, the diagnosis can be based upon clinical judgment if history and physical examination findings are consistent with EMS, or a CGIT can be performed.

Resting glucose and insulin concentrations: Most ponies or horses with chronic IR are able to maintain normoglycemia, but this is accomplished by increasing insulin secretion from the pancreas, which results in hyperinsulinemia. Resting blood glucose and insulin concentrations can therefore be measured to screen horses for IR. This test is highly recommended and can be combined with ACTH measurements in older patients with suspected PPID (refer to **Chapter 3**).

Insulin assays vary between laboratories, so the reference range for your referral laboratory must be used. It is also important to select a laboratory that routinely measures insulin in equine blood samples and has established reference ranges for horses. Our laboratory uses a radioimmunoassay manufactured by Diagnostic Products Corporation (Siemens Healthcare, Deerfield, Illinois) and hyperinsulinemia is defined by a serum insulin concentration greater than 20 µU/mL (mU/L; multiply by seven to convert to pmol/L) if the blood sample is collected after feed deprivation (fasting). If hay has been fed, a cut-off value of 30 µU/mL can be used to define IR, but it is advisable to recheck the patient after feed deprivation. Our approach to interpreting test results is outlined in **Table 4.1**.

If hyperglycemia is detected, it raises concern about the progression of chronic IR into pancreatic exhaustion and type 2 diabetes mellitus. Type 2 diabetes mellitus is rare in the horse, but occasionally occurs and can be confirmed by detecting glucosuria. Horses with advanced PPID sometimes develop this problem and may require higher dosages of pergolide.

Testing protocol

Testing should be delayed until after laminitis has subsided because pain and stress will raise blood glucose and insulin concentrations. Horses should also be given time to acclimate if they have been transported to a hospital for testing. If the horse is being evaluated in the field, blood should be collected as soon as the veterinarian arrives on the farm, before the horse becomes agitated by this or any other procedure.

The horse must be held off pasture and feed should be withheld for six hours before sample collection. Owners should be instructed to leave their horse with one flake of hay after 10:00 PM the night before and then hold the animal off feed until blood has been collected the next morning. However, we have recognized that certain horses become very agitated when feed is withheld, so these patients should be allowed to eat hay to prevent stress. Clients should be asked to delay feeding all of the horses in the barn until after samples because the horse undergoing testing may become agitated if other horses are fed in the morning.

Table 4.1 Guidelines for interpreting resting glucose and insulin concentrations in blood samples collected after feed deprivation

Glucose (mg/dL)	**Insulin** (µU/mL)	**Interpretation***
< 100	< 20 (Hay: <30)	No evidence of insulin resistance at this time Retest at another time of the year or perform the combined glucose-insulin test (CGIT) if the equine metabolic syndrome (EMS) phenotype is recognized Address any problems with obesity
< 100	> 20	Normoglycemia with hyperinsulinemia Horse suffers from compensated insulin resistance; there is an increased risk of laminitis Recommend weight management plan, diet changes, and exercise
< 100	> 100	Normoglycemia with marked hyperinsulinemia Severe compensated insulin resistance; high risk of laminitis Strictly control diet and consider pharmacological intervention
> 100	> 20	Horse is losing its ability to regulate glucose because pancreatic insufficiency is developing Transitioning from compensated to uncompensated insulin resistance; high risk of laminitis Test for pituitary pars intermedia dysfunction (PPID)
> 120	< 20	Glucose levels are unregulated and pancreatic insufficiency has developed Horse suffers from uncompensated insulin resistance; high risk of laminitis Check urine glucose for evidence of diabetes mellitus and test for PPID

*Patient is not pained or stressed; all feed withheld for 6 hours prior to sampling

Glucose to insulin ratio (G:I ratio): This ratio is calculated by dividing the glucose concentration in mg/dL by the insulin concentration in µU/mL (or mU/L). The correct units must be used, so glucose concentrations reported in mmol/L must be multiplied by 18 and insulin concentrations reported in pmol/L have to be divided by 7. The guidelines for interpreting results are that IR is present when the ratio is below 10 and severely insulin-resistant horses have ratios less than 4.5. If we assume a glucose concentration of 90 mg/dL, these cut-off values are equivalent to serum insulin concentrations of 9 and 20 µU/mL, respectively.

The G:I ratio is *not recommended* because it leads to the over-diagnosis of IR and fails to recognize all forms of the disorder. Insulin results vary between laboratories, depending upon the testing procedure used, so some report higher insulin values than others, even when the same blood sample is submitted. This creates a problem when the G:I ratio is used because reference ranges are not taken into account. Glucose concentrations also decrease in samples if there is a delay between collection and submission, and this lowers the ratio. Finally, a horse that suffers from hyperglycemia will have a higher ratio, which makes the situation look better, even though the pancreas is failing and diabetes mellitus is developing.

Proxy measurements: These values can be calculated from blood glucose and insulin concentrations to predict the risk of IR. The two proxies used are the *reciprocal of the square root of insulin* (RISQI) and the *modified insulin-to-glucose ratio* (MIRG). The RISQI represents the degree of insulin sensitivity (a low number indicates IR) and the MIRG represents the ability of the pancreas to secrete insulin (most horses with IR have higher values). The RISQI value is more important and can be easily calculated. Divide 1 by the square root of the insulin concentration to obtain the RISQI value. A RISQI less than 0.29 indicates IR, which is equivalent to a serum insulin concentration of 12 µU/mL. In this author's opinion, this cut-off value for IR is too low because healthy Quarter Horses and Tennessee Walking Horses often have serum insulin concentrations above 12 µU/mL. This method of assessing horses and ponies is an effective research tool when used under controlled conditions, but is *not recommended* for the evaluation of patients in practice.

Combined glucose-insulin test (CGIT): This dynamic test is useful for detecting IR in patients with the EMS phenotype that have normal blood glucose and insulin concentrations.

Testing protocol

Stress induces false positive results when the CGIT is used, so testing must be delayed until after laminitis has improved. If the test is performed at a referral hospital, the horse must be given several days to acclimate to the surroundings and the intravenous catheter should be placed the night before. Testing can be performed on the farm, with the catheter inserted on the same day, but the horse must remain calm throughout the procedure. Horses should be kept off pasture and deprived of feed for six hours prior to testing. However, some horses become very agitated when deprived of feed, so they can be fed before and during the procedure. Tranquilizers also induce IR, so they cannot be given within 12 hours of testing.

A pre-infusion blood sample is collected for baseline glucose and insulin measurements, and then 150 mg/kg body weight (bwt) 50 percent dextrose solution is infused, immediately followed by 0.10 units/kg bwt regular insulin (Humulin R®, Eli Lilly, Indianapolis, Indiana).[13] These dosages are equivalent to 150 mL of 500 mg/mL (50 percent) dextrose and 0.50 mL of 100 units/mL regular 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 percent NaCl) prior to infusion. Blood glucose concentrations are measured using a hand-held glucometer at 1, 5, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135, and 150 minutes post-infusion. A blood sample must also be collected at 45 minutes and submitted for a second insulin measurement. The test can be abbreviated to 60 minutes when used in the field, but it is advisable to complete the measurements so that the complete response can be recorded.

Insulin resistance is defined by blood glucose concentrations remaining above baseline for more than 35 minutes, or by the detection of a serum insulin concentration above 100 µU/mL at 45 minutes. The time taken for the blood concentration to return to baseline is recorded, and an example is provided in **Figure 4.7**. Two 60 mL syringes containing 50 percent dextrose solution should be prepared in case clinical signs of hypoglycemia (sweating, weakness) are seen, or the glucose concentration drops below 40 mg/dL (2.2 mmol/L).

A hand-held glucometer is used for this procedure and these devices can be purchased at drug stores. They are used by people with diabetes that have to monitor their blood glucose levels. The Medisense Precision QID® glucometer manufactured by Abbott Laboratories, Inc. has been used by our research group and only costs approximately $65. However, the AlphaTRAK® (Abbott Laboratories, Inc.) glucometer is now available for veterinary use and it has been shown to be more accurate when used in dogs. The start-up kit for this glucometer costs approximately $180.

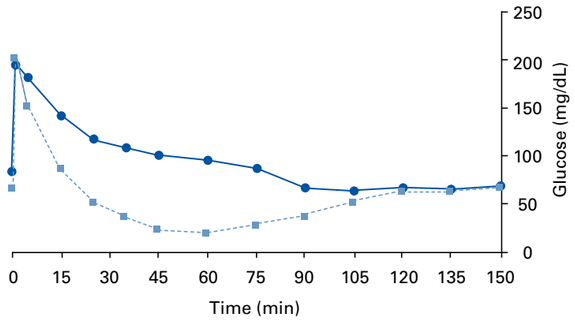


Figure 4.7 Blood glucose concentrations in an insulin sensitive horse that returned to baseline by 25 minutes (squares; dashed line) and an insulin-resistant horse that remained above baseline until 90 minutes (diamonds; solid line)

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CHAPTER 5

Management of Insulin Resistance

Dr. Nicholas Frank

A client information sheet has been provided and can be found in ***Appendix 2****.*

Dietary management of insulin resistance

Management of IR involves three approaches: 1) reducing the sugar and starch content of the feeds provided to the horse, 2) limiting or eliminating access to pasture until IR improves, and 3) increasing exercise. The first approach involves selection of hay that has a lower sugar and starch content, which can be determined by submitting a sample for analysis. Equi-analytical Laboratories (or its partner company Dairy One Forage Laboratory) analyzes hay and provides starch, ethanol-soluble carbohydrate (ESC), and water-soluble carbohydrate (WSC) content. Ethanol-soluble carbohydrates include simple sugars such as monosaccharides and disaccharides, whereas WSC measurements also include fructans. The laboratory can be contacted at 1-877-819-4110 or www.equi-analytical.com and testing costs approximately $35 per sample.

The non-structural carbohydrate (NSC) content of the hay should be calculated from the values provided by the laboratory. However, clinicians and researchers disagree about the appropriate method of calculating NSC content. Some think that the WSC content of the hay is important, whereas others argue that fructans should be excluded because they are not absorbed in the small intestine and would not be expected to contribute to the rise in blood glucose concentrations after a meal.

At present, we recommend that NSC be calculated by adding starch and ESC together, and this level should ideally fall below 10 percent as fed. However, the relative importance of NSC content varies, depending upon the severity of IR. Horses with severe IR (resting insulin concentration greater than 100 µU/mL) must be maintained on a stringent diet with a NSC content less than 10 percent, whereas mildly affected animals can be fed hay with higher levels. If hay has already been purchased and the NSC level is between 10 and 12 percent, soaking the hay in cold water for 60 minutes before feeding will reduce the sugar content.

Horses with both PPID and IR are challenging to manage from a dietary standpoint if skeletal muscle atrophy has developed and the animal is underweight. More calories must be provided without exacerbating IR. This can be accomplished by feeding one of the commercial low-sugar/low-starch (low-NSC) pelleted feeds that are now available to horse owners. These feeds vary in their NSC content, so the

severity of IR must be taken into account before one is selected. It is also better to divide the daily ration into multiple small meals and to feed hay beforehand to slow gastric emptying. These strategies are employed to lower the glycemic response to the 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, so insulin concentrations should be rechecked 7 to 14 days after a new diet has been initiated.

Severely insulin-resistant horses are particularly difficult to manage and may require individual diet formulation. Molasses-free beet pulp can be fed to these horses because this feed has a low glycemic response, yet provides calories through hindgut fermentation and volatile fatty acid production. A listserve (pets.groups.yahoo.com/group/EquineCushings), organized by Dr. Eleanor Kellon (a veterinarian and private nutritionist), is a source of support and useful information for horse owners that are struggling with the management of individual animals.

Pasture access must be restricted or eliminated until insulin sensitivity has improved and this is important for two reasons. First, carbohydrates consumed on pasture can trigger gastrointestinal events that trigger laminitis in susceptible insulin-resistant horses and second, pasture grass is an unregulated source of starch and sugar. These carbohydrates can continue to exacerbate IR, even when other aspects of the diet have been regulated.

Exercise

Exercise is an important strategy for improving insulin sensitivity and maintaining skeletal muscle mass because atrophy reduces the mass of insulin-sensitive tissue within the body. Any form of exercise is likely to be beneficial, even simply walking the horse on a lead rope. Insulin resistance sometimes resolves after a regular riding schedule is initiated.

Dietary management of obesity

Weight loss should be induced in obese horses by restricting the total number of calories consumed. In horses that are being overfed, removal of all concentrates from the diet is often sufficient to induce weight loss. However, it may be necessary to restrict caloric intake even further in some obese horses and this is accomplished by controlling hay intake. An obese horse should be placed on a diet consisting of hay fed in an amount equivalent to 2 percent of current body weight (e.g., 24 pounds hay per day for a 1,200-pound horse), and then this amount should be lowered to 1.5 percent of current body weight, and finally to 1.5 percent of ideal

body weight (15 pounds hay for an ideal weight of 1,000 pounds). Hay should be weighed on scales to ensure that correct amounts are fed. It is often difficult to induce weight loss when horses are turned out on pasture, so access to pasture should be denied until an ideal body condition has been reached.

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. Grass is also an unregulated source of starch and sugar, so these carbohydrates will continue to exacerbate IR even when other aspects of the diet have been controlled. 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 sugars.[1] Strategies for limiting grass consumption include short (less than one hour) turnout periods, confinement in a small paddock, round pen, or area enclosed with electric fence, or use of a grazing muzzle. 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. A balanced vitamin and mineral supplement should be provided to horses that are housed off pasture. One specific recommendation is to provide 1,000 IU vitamin E per day in the form of a supplement.

Medical management of obesity-associated insulin resistance

Most horses or ponies with EMS can be effectively managed by controlling the horse's diet, instituting an exercise program, and limiting or eliminating access to pasture. However, there are times when these strategies will not improve the situation fast enough to prevent additional episodes of laminitis. In these situations, drug therapy is warranted to lower the likelihood of subsequent laminitis episodes that could cause permanent damage to the feet.

Levothyroxine sodium

Weight loss can be accelerated and insulin sensitivity improved in obese insulin-resistant horses and ponies by administering levothyroxine sodium (Thyro-L®, LLOYD, Inc., Shenandoah, Iowa). Levothyroxine sodium is administered to horses as a powder (Thyro-L®) and one teaspoon provides 12 mg levothyroxine sodium. We have performed four research studies to evaluate the use of this drug in horses:

Initial investigation to establish drug efficacy and dosage

In this initial study, we administered levothyroxine to eight healthy mares according to an incrementally increasing dosing regimen over an eight-week period.[2] Mares received 24 mg (2 tsp), 48 mg (4 tsp), 72 mg (6 tsp), or 96 mg (8 tsp) for two weeks at a time. Mean body weight decreased and insulin sensitivity increased in treated mares.

Long-term study of efficacy and safety

Our second study evaluated the long-term effects of the drug on body weight and insulin sensitivity in six healthy mares over a 12-month period.[3,4] Levothyroxine was administered at a dosage of 48 mg (4 tsp) per day and glucose dynamics were measured at 0, 4, 8, and 12 months. Echocardiographic evaluations, complete blood count, and plasma biochemical analyses were also performed at the same times to assess the safety of levothyroxine. Body weight decreased again in response to treatment and this alteration was mirrored by a greater than twofold increase in mean insulin sensitivity. No adverse health effects were detected.

Evaluation of levothyroxine as a treatment for obesity-associated insulin resistance

This is an ongoing study that has been funded by the US Equestrian Federation, Grayson Jockey Club Foundation, and LLOYD, Inc. We are determining the effects of Thyro-L® (48 mg/day) on body weight and insulin sensitivity in horses affected by EMS.

Our preliminary results show that obese insulin-resistant horses lose weight and show a reduction in neck circumference when treated with Thyro-L®. Horses (n = 4) on a controlled diet exhibited a 5 cm decrease in mean neck circumference over 6 months, whereas the same measurement decreased by 10 cm in treated horses (n = 4). We have subjectively observed that the neck crest softens in treated horses and this finding precedes the reduction in neck circumference. In our preliminary study, both treated and control horses showed an improvement in insulin sensitivity as they lost weight, and weight loss appeared to be accelerated in horses treated with Thyro-L®.

Measured serum total thyroxine (tT_4) concentrations are elevated when levothyroxine is administered at the 48 mg (4 tsp) per day dosage, but these concentrations vary considerably within and between horses. Serum tT_4 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 sweating or tachycardia have not been observed in treated horses.[2,5,6]

When levothyroxine treatment is discontinued, horses should be weaned off the drug by lowering the dosage to 24 mg (2 tsp) per day for two weeks and then 12 mg (1 tsp) per day for two weeks. The benefit of treating horses with levothyroxine at lower dosages for longer periods has not been evaluated scientifically.

Pre-treatment with levothyroxine ameliorates endotoxin-induced insulin resistance

This work has been supported by the American Quarter Horse Foundation and focuses upon the effects of endotoxemia on insulin sensitivity in horses. Endotoxemia lowers insulin sensitivity and this may play an important role in the exacerbation of IR that occurs in grazing horses that undergo intestinal events. We have previously established that endotoxemia induces transient IR in horses,[7] but results of our recent study have shown that the resting insulin sensitivity of the horse prior to endotoxin administration determines the magnitude of the IR that develops afterwards. Interestingly, healthy horses that were treated with levothyroxine sodium (Thyro-L®, LLOYD, Inc., Shenandoah, Iowa) for 14 days did not show an increase in insulin sensitivity over this short time period, but lost body weight, and most importantly, did not develop IR following endotoxin administration. Results of this work have recently been presented as an abstract at the 2008 American College of Veterinary Internal Medicine (ACVIM) Forum.

Prescribing Thyro-L® to patients

It is essential for horses to be placed on a controlled diet when levothyroxine sodium is administered because we have subjectively observed that feed intake increases in response to treatment. Weight loss is unlikely to be achieved if the horse is allowed free access to pasture and the owner will perceive this as a treatment failure. Thyro-L® is given by mouth or in the feed at a dosage of 48 mg per day for three to six months to induce weight loss, which is equivalent to 4 tsp per day. 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 2 teaspoons (24 mg) orally per day for two weeks and then 1 teaspoon (12 mg) orally per day for two weeks.

Medical management of insulin resistance in lean horses

Insulin sensitizing drugs including metformin and supplements such as chromium and magnesium are being evaluated as treatments for IR in horses.

Metformin

Positive responses to metformin have recently been reported.[8] This drug is available as Glucophage® (Merck Santé S.A.S., Darmstadt, Germany) and is distributed

in the United States by Bristol-Myers Squibb Company. In the aforementioned study, metformin was administered to insulin-resistant horses and ponies at a dosage of 15 mg/kg twice daily by mouth. Insulin sensitivity improved in treated animals, without the adverse effect of hypoglycemia, but long-term results were variable.

Metformin is a biguanide drug that enhances the action of insulin within tissues at the post-receptor level and inhibits gluconeogenesis within the liver. Results of this first study look promising and metformin represents an option for the short-term management of leaner insulin-resistant horses. However, 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 efficacy may be improved by administering metformin three times daily (personal communication, Dr. Anna Firshman, June 2008), but further studies are required.

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CHAPTER 6

Perspectives on Laminitis

Dr. Nicholas Frank

There are different ways to describe the laminitis that we associate with endocrine disorders. In this chapter, we will examine some of the potential links between the metabolic status of the horse and its susceptibility to laminitis. These mechanisms have yet to be determined, but we can draw upon results of studies performed in other animals to speculate about the situation in horses.

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 increases the risk of laminitis or if IR is the important factor. Obesity and IR are associated in horses,[1] 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 alpha (TNFα) is secreted from adipose tissues as body mass index increases.[2] This inflammatory cytokine inhibits insulin receptor signaling, which lowers insulin sensitivity. Vick et al.[3] found that blood TNFα mRNA expression was higher in obese horses and our research group has detected elevated TNFα mRNA expression within adipose tissues collected from obese insulin resistant horses (unpublished data). 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 describing laminitis that develops in horses with endocrine disorders. This includes laminitis associated with obesity, IR, PPID (also called equine Cushing's disease), or corticosteroid administration.

Equine metabolic syndrome 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 appears 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.

Pituitary pars intermedia dysfunction 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.[4] More research is required to determine whether horses with PPID are predisposed to laminitis because corticosteroid excess weakens hoof tissues over time or if IR is the key determinant of laminitis risk in these patients.[5] Johnson et al.[5] 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 appears 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 to 20 years) as obese horses begin to retain their winter haircoat and then 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 following 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.[6] 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.

Relating insulin resistance 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.[7] 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. Nitric oxide 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.[8] detected an increase in plasma ET-1 concentration within blood collected from digital veins 12 hours 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, then 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.[9] detected higher mRNA expression of intracellular adhesion molecule (ICAM) and E-selectin within laminar tissues collected 1.5 hours 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.[9] 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[10] and it is likely that chronic IR enhances these processes. Weiss et al.[11] 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.[10] and Menzies-Gow et al.[12,13] have demonstrated 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.[12,13] 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.[7] 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.[14] Digital arteries within the equine limb are 30 to 40 times more sensitive to vasoconstrictors such as serotonin, which suggests that platelet-derived mediators have more profound effects on the laminar blood supply.[15,16] 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 endothelium-derived NO modulates the response to vasoconstrictors within the vasculature of the equine digit.[17]

Capillary recruitment

Chronic IR may have other effects on the vasculature because insulin is involved in capillary recruitment.[7] In humans, ingestion of a meal is associated with increased blood flow to limbs and decreased vascular resistance.[18] Terminal arterioles dilate, which increases the number of capillaries that are perfused. This is referred to as capillary recruitment and it is a physiological mechanism that enhances glucose delivery to myocytes.[7] In one study performed in humans, microvascular volume within the forearm increased by 45 percent one hour after eating a meal.[18] Insulin resistance impairs the process of skeletal muscle capillary recruitment and contributes to the development of hyperglycemia in humans.[19] 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.[20] These anastomoses may be affected by chronic IR.

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.[21] It should also be recognized that obese horses carry more weight on their hooves, which increases the forces exerted upon dermoepidermal 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).[22] 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.[22] Tumor necrosis factor alpha 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.[21]

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.[23] Adiponectin enhances insulin sensitivity, so lower plasma concentrations are also associated with IR.[23] Endothelium-dependent vasodilation may also be compromised when adiponectin concentrations are low and this might contribute to the pro-inflammatory state induced by obesity.[21]

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.

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 investigated the predisposing factors for pasture laminitis and demonstrated that insulin resistant ponies are more likely to develop disease.[6] 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.

An insulin resistance crisis

This theory is supported by results of a recent study in which Asplin et al.[24] induced laminitis in clinically normal ponies by infusing insulin and glucose intravenously for up to 72 hours. Intravenous infusion of insulin caused profound hyperinsulinemia in the five treated ponies and the mean time for laminitis to develop was 33 hours. 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 prior to laminitis developing. However, healthy nonobese 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, then 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 corn starch and wood flour directly into the stomach using a nasogastric tube.[8,25] Both approaches accomplish the same goal of altering the microbial flora, enhancing lactic acid production, lowering the intraluminal pH, and increasing intestinal permeability.[8,26] Exotoxins, endotoxins, vasoactive amines, or other bacterial by-products subsequently move into the blood and initiate a systemic inflammatory response that triggers laminitis.[14] The events following 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.[27] 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.[14] Endotoxemia and laminitis have been associated in a retrospective study of hospitalized horses,[28] but the disease has never been induced by administering exogenous lipopolysaccharide to horses.[12]

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.[29] 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.

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CHAPTER 7

Pasture-associated Laminitis in Horses and Ponies

Dr. Ray Geor

Introduction

Laminitis is a painful and debilitating condition of horses and ponies that has major economic and welfare implications.[1,2] By the time clinical signs are recognized, significant damage has occurred to the hooves and treatment options are limited.[1] According to a general survey in the USA, apart from colic, laminitis is the most common reason a horse or pony will be presented for veterinary treatment and 13 percent of horse owners/operations reported problems with laminitis in their horses over the previous 12 months with approximately five percent of those affected by laminitis dying or being euthanized.[3] Although epidemiological studies are lacking, there is general agreement among veterinarians and horsemen that the majority of cases occur in animals kept at pasture (hence the term ***pasture-associated laminitis***). In one survey in the United Kingdom, 61 percent of laminitis cases occurred in animals kept at pasture,[4] while the results of the 1998 National Animal Health Monitoring System (NAHMS) laminitis study demonstrated that 46 percent of cases were associated with grazing on pasture.[3]

This review considers current knowledge on the epidemiology and pathogenesis of pasture-associated laminitis, including the role of forage carbohydrates and metabolic predispositions. Feeding management strategies for disease avoidance in susceptible animals are also discussed.

Epidemiology and risk factors

Anecdotal observations have indicated that pasture-induced laminitis occurs at times of rapid grass growth and the accumulation of certain carbohydrates (fructans, starches and/or sugars) in pasture forage, i.e., during the spring and early summer, and during the fall. Surprisingly, very few studies have examined the effect of time of year on the incidence of laminitis. Some of these studies[3-5] have shown an increased risk during spring and summer, while others have failed to demonstrate an association between season and the occurrence of acute laminitis.[6,7] However, the latter studies involved referral populations that may not have accurately reflected disease incidence in the general population.

In the 1998 NAHMS survey study, laminitis accounted for approximately 20 percent of foot problems in the winter, whereas about 40 percent of these problems were attributed to laminitis in the spring and summer.[3] A three-year retrospective study of pasture kept horses and ponies in a specific region of the UK found that approximately 20 percent (291/1,451) of the total population had at least one episode of laminitis.[5] This study also provided evidence to support the clinical observation that the disease tends to be recurrent in certain individuals. Specifically, 35 percent of the animals diagnosed with laminitis had repeated episodes over the total study period, with many animals diagnosed multiple times within the same year. The highest prevalence (2.39 percent) and incidence (16 cases/1,000 animals) occurred in May. There was a statistically significant positive association between hours of sunshine and incident laminitis, but laminitis prevalence and incidence were not associated with regional rainfall or ambient temperature. Presumably, this association between hours of sunshine and incident laminitis reflects altered nutritional intake (i.e., increased consumption of forage carbohydrates during periods of bright sunshine that promote plant photosynthesis and carbohydrate accumulation) rather than the direct effect of exposure of horses to sunlight. The putative role of forage carbohydrates in the pathogenesis of pasture-induced laminitis is discussed below (see *Pathogenesis of Pasture Laminitis*).

Another important aspect of pasture laminitis is the clinical observation that certain horses or ponies tend to be affected more than others—with susceptible animals often prone to recurrent episodes. This raises the possibility that there are phenotypic or genetic factors that confer susceptibility or resistance to disease. The mechanisms underlying this predisposition are not understood and this area is currently under investigation by several research groups. However, there is gathering evidence implicating metabolic factors, particularly obesity, insulin resistance (IR) and hyperinsulinemia, as major predisposing conditions for pasture laminitis.[8] Individual variation in tissue (e.g., laminar epithelium, digital vasculature) response to trigger factors or in hindgut bacterial flora and their response to dietary substrates also may play a role, but there is minimal information in these areas. Differences in appetite and forage intake are other possible factors.

Clinical observations have long suggested that horses and ponies with a particular phenotype are predisposed to pasture-associated laminitis.[9] These animals fit the description of an easy keeper and are often obese (and/or have regional adiposity, such as a cresty neck) and persistently hyperinsulinemic. The term ***equine metabolic syndrome*** (EMS) has been adopted to describe horses and ponies with evidence of generalized or regional adiposity, hyperinsulinemia and subclinical (i.e., hoof founder rings) or overt laminitis. Clinical observations linking IR and laminitis predisposition are supported by results of observational cohort studies in ponies. In an inbred herd of Welsh and Dartmoor ponies,

the clustering of IR, hyperinsulinemia, obesity and hypertriglyceridemia was associated with predisposition to pasture laminitis.[8] The term ***prelaminitic metabolic syndrome*** (PLMS) was used to describe these ponies. The PLMS criteria predicted 11 of 13 cases of clinical laminitis observed in May of the same year, with an odds ratio of 10.4, i.e., ponies with this insulin resistant phenotype were at approximately ten times higher risk for development of laminitis. Another study of out-bred ponies in the UK confirmed the association between IR and predisposition to pasture laminitis, and provided evidence of hypertension in the high risk ponies.[10] Interestingly, signs of this metabolic syndrome (i.e., IR and hypertension) were evident in summer but not winter, suggesting that consumption of summer pasture forage may induce abnormal metabolic responses leading to the expression of the prelaminitic phenotype. It is worth mentioning that insulin sensitivity is markedly lower in ponies when compared to horse breeds, potentially explaining the apparent higher susceptibility of pony breeds to pasture laminitis reported in some epidemiological studies.[4,5]

There are minimal published data on the possible association between IR and pasture-induced laminitis in horses. Nonetheless, the EMS phenotype has been described in several breeds, notably Morgans, Paso Finos, Arabians and Norwegian Fjords, and many of these horses are out on pasture when laminitis is first detected (Frank 2007). Insulin resistance also may contribute to laminitis predisposition in ***pituitary pars intermedia dysfunction*** (PPID), also known as ***equine Cushing's disease***. In clinical reports, chronic, insidious onset laminitis has been described in more than 50 percent of horses or ponies diagnosed with PPID. Hyperglycemia, hyperinsulinemia and glucose intolerance, findings consistent with IR, have been described in horses with PPID.[11] Interestingly, in one report hyperinsulinemia was associated with poor long-term survival in horses with suspected PPID.[12]

There is evidence that obesity and/or regional adiposity predisposes horses and ponies to laminitis. In a prospective case-control study of 258 cases seen at six veterinary teaching hospitals, a cresty neck was found in significantly more cases than controls.[13] In our own studies at Virginia Tech, ponies and horses at higher risk for pasture laminitis had higher body condition scores (BCS greater than seven) compared to animals without a history of laminitis. Regional adiposity, particularly a cresty neck, also was common in these animals. Mechanical trauma due to the increased load on the feet is one theory linking obesity with laminitis risk, but the increased risk of laminitis in obese equids is more likely related to development of IR. Several studies have demonstrated an association between adiposity and IR in horses. However, it is important to recognize that 1) not all obese horses are insulin resistant, and 2) IR can occur in nonobese animals. Therefore, clinical evaluation of adiposity alone is not sufficient for assessment of risk for pasture-associated laminitis.

Several authors have proposed that one or more genetic polymorphisms underlie the metabolic syndrome that predisposes to pasture laminitis.[8,10] In the Welsh and Dartmoor pony herd studied by Virginia Tech, pedigree analysis suggested a dominant mode of inheritance for the PLMS phenotype, supporting the possibility of a genetic basis for the IR and laminitis predisposition in this population.[8] Further studies in more out-bred populations are required to confirm these findings. Nonetheless, it is tempting to speculate that these susceptible ponies have a "thrifty genotype" where, at least in part, the IR is an adaptive strategy for survival in nutritionally sparse environments. However, this strategy may fail when these animals are exposed to high carbohydrate diets, with development of obesity, exacerbation of IR and hyperinsulinemia and increased risk of laminitis. A similar scenario may contribute to the suggested increased susceptibility of easy keeper horses (e.g., Morgan, Arabians, Paso Fino, and Spanish Mustang breeds) to pasture-associated laminitis.

Pathogenesis of pasture laminitis

Ingestion of pasture forage rich in nonstructural carbohydrates (NSC; which include simple sugars and the more complex storage carbohydrates: starches and fructans) has been implicated in the development of laminitis. Laminitis may be linked to pasture grass NSC content by two mechanisms: 1) the intake of large loads of rapidly fermentable NSC with induction of gastrointestinal disturbances that trigger disease, and 2) exacerbation of IR and hyperinsulinemia in predisposed animals with a lowering of the threshold for laminitis.

Laminitis can be induced experimentally by the administration of large doses (approximately 17 g/kg bwt) of starch[1] that exceed the digestive capacity of the small intestine, with overflow of undigested starch into the hindgut. Similarly, the administration of oligofructose (7.5-12 g/kg bwt), a fructan extracted from the root tubers of chicory, results in laminitis approximately 24 to 48 hours after dosing.[14] As fructans are thought not to be digested by mammalian enzymes, it is probable that much of the administered dose passes into the large intestine undigested.[15] The delivery of this undigested, rapidly fermentable substrate (starch or fructan) to the hindgut initiates changes in the bacterial flora, with proliferation of Gram positive organisms, especially lactic acid-producing lactobacilli and streptococci, leading to a decrease in the intraluminal pH and an increase in intestinal permeability. These alterations in the hindgut environment are thought to result in the production and absorption of laminitis triggering factors (e.g., vasoactive amines,

exotoxins and endotoxins) with damage to the laminae when these circulating compounds alter digital blood perfusion, create local inflammation, or stimulate excessive matrix metalloprotease activity.[1]

Nonstructural carbohydrate accumulation in pasture plants—Implications for laminitis

At certain times of the year, the quantity of pasture NSC ingested by grazing equids may approach or exceed the amount of starch or fructan known to induce laminitis when administered as a single dose.[15] Pasture plants contain varying levels of simple sugars, fructans and starch. The vegetative tissues of temperate (cool season or C3) pasture grasses such as perennial ryegrass or fescue accumulate fructan as the primary storage carbohydrate, with most fructan stored in the stem until required by the plant as an energy source. In contrast, starch is the storage carbohydrate of the seed of temperate grasses and the seed and vegetative tissues of legumes (e.g., clover) and warm season (C4) grasses such as Bermuda. The type of fructan varies between grass species. The fructan in perennial ryegrass has lower molecular weight (shorter chain-length) when compared to that in timothy or orchard grass species. In vitro studies have shown more rapid fermentation of the lower molecular weight fructans in ryegrass, suggesting that this species may pose the highest risk for pasture-associated laminitis.

A large number of environmental factors influence NSC accumulation in pasture plants; these include the intensity and duration of sunlight, temperature (ambient and soil), soil fertility, water availability, and nitrogen status.[15] Studies in several Northern European countries have shown fructan content of perennial ryegrass to vary between less than 100 g and greater than 400 g/kg of dry matter (DM) depending on the season and growing conditions. In general, pasture NSC is highest in spring, lowest in mid-summer and intermediate in the fall. For example, in pastures (tall fescue, Kentucky bluegrass mix) at Virginia Tech's MARE Center, NSC content is highest in April and May (greater than 15 to 20 percent DM, i.e., 150 to 200 g/kg), intermediate in the fall, and lowest in mid-winter and summer (less than five to seven percent DM). However, there also can be marked daily fluctuations that coincide with patterns of energy storage (photosynthetic activity) and utilization. Thus, pasture NSC tends to rise during the morning, reaching maxima in the afternoon and then declining overnight. Therefore, horses grazing in the afternoon, when compared to nighttime or the morning, may ingest between two and four times as much NSC. Stress conditions that restrict plant growth (and therefore energy demands) result in accumulation of NSC. These stress conditions include low temperatures, killing frosts, applications of non-lethal herbicides and low soil fertility.

For horses with 24-hour access to pasture, daily pasture intake likely ranges between two percent to three percent of bodyweight (as DM), or 10 to 15 kg DM intake for a 500-kg horse. Thus, NSC intake would range between 0.75 and 1.5 kg DM per day and 2.25 and 4.5 kg DM per day for, respectively, pastures with NSC content of 100 and 300 g/kg DM. The higher end of pasture NSC intake approaches the amount of starch or fructan known to induce digestive disturbances and laminitis, albeit consumed over a 12 to 17 hour period rather than as a bolus. It is possible that the dosage of NSC (e.g., as fructan) required to trigger digestive and metabolic disturbances in susceptible animals (i.e., a horse or pony with an insulin resistant phenotype) is considerably lower than that needed to reliably induce disease in healthy experimental animals. Alternatively, laminitis prone animals may preferentially graze areas of pasture high in NSC. A further possibility is that susceptible horses and ponies have differences in their gut flora compared with non-laminitic animals, with heightened hindgut fermentative responses to a given load of NSC and increased production of trigger factors. However, the decrease in fecal pH associated with the feeding of inulin (3 g/kg bwt) did not differ between normal ponies and those predisposed to laminitis.[16]

Role of insulin resistance and hyperinsulinemia

A second potential mechanism linking the consumption of pasture forage NSC to laminitis is exacerbation of IR and hyperinsulinemia in predisposed animals with a lowering of the threshold for disease. Certainly, there is evidence that adaptation of weanling or mature horses to concentrates rich in starch and sugar results in a decrease in insulin sensitivity.[17] Recent studies in our laboratory have shown a strong relationship between pasture NSC and circulating insulin concentrations in horses, with exacerbation of IR and hyperinsulinemia in laminitis-prone ponies when they are grazing spring pasture rich in NSC. In a single herd of Welsh and Dartmoor ponies, some of which are insulin resistant and prone to recurrent pasture laminitis, serum insulin concentrations markedly increased during the months of April and May when ponies were grazing on pasture in Virginia, and this occurrence coincided with an increase in pasture grass NSC content (unpublished data). Furthermore, nine ponies from the laminitis prone group developed laminitis seven to ten days after hyperinsulinemia was detected. Similarly, feeding inulin (to simulate intake of fructan from spring grass) to ponies elicits an exaggerated insulin response in animals predisposed to laminitis.[18] This exacerbation of IR and hyperinsulinemia in the face of increased NSC intake is likely to lower the threshold for laminitis, perhaps explaining why susceptible animals succumb to laminitis at certain times of the year, depending on dietary intake of starch, sugar and/or fructan contents. Endotoxemia with secondary disturbances in the hindgut microenvironment is one factor that could exacerbate pre-existing IR

in association with increased NSC intake from pasture forage. In healthy horses, IV administration of lipopolysaccharide (20 ng/kg bwt) decreased insulin sensitivity and increased the pancreatic insulin response to a glucose load.[19]

Insulin resistance is likely to predispose horses and ponies to laminitis by altering vascular dynamics and impairing the ability of the hoof vasculature to respond to challenges. Insulin is a vasoregulatory hormone, invoking vasodilatation through pathways similar to those of insulin-mediated glucose metabolism.[20] In insulin resistant states, insulin's ability to counteract endothelin-1 associated vasoconstriction may be compromised due to decreased nitric oxide synthesis, while compensatory hyperinsulinemia might stimulate increased endothelin-1 production. Previous studies have shown that endothelin-1 concentrations are higher in laminar connective tissues from horses with laminitis.[21]

It is also possible that hyperinsulinemia per se induces disease in susceptible animals. This is supported by results of a recent study in which acute laminitis was experimentally induced in ponies by infusing exogenous insulin to cause marked hyperinsulinemia (greater than 1,000 mU/L).[22] Ongoing studies are exploring the mechanism(s) by which hyperinsulinemia induces lamellar failure.

Case management

A diagnosis of laminitis is based on signs of lameness, pain upon application of hoof testers in one or more feet, heat in the hoof walls and increased digital pulses. The reader is referred to the chapter by Dr. Steve Adair in this guide for a detailed discussion on medical management of laminitis. In brief, the primary goals of management are to alleviate pain and discomfort, minimize structural changes within the hooves, and restore function without further compromising structural integrity of the hoof. Affected animals should be removed from pasture and confined to a box stall (or other small area) that has been deeply bedded. Lateral digital radiographs are recommended to assess rotation of the pedal bone. Horses should remain in confinement for at least two to three weeks following an episode of acute laminitis. A longer period of confinement may be required in severely affected animals with marked pedal bone rotation in one or more feet.

Affected animals should be carefully assessed for evidence of prior episodes of laminitis as well as underlying metabolic and endocrine abnormalities (i.e., EMS and PPID). There may be history of prior episodes of pasture-associated laminitis and/or hoof wall "founder lines" indicative of previous episodes. Evaluation of insulin sensitivity (refer to Chapter 4) is indicated but testing should be delayed until after resolution of the acute laminitic episode because laminitis-associated pain and stress will confound test results. Another important issue to be addressed is whether or not affected animals should be allowed to return to pasture after resolution of the laminitis episode. These aspects are discussed in the next section.

Avoidance of pasture laminitis in high-risk animals

For horses or ponies with a history of recurrent laminitis and/or clinical evidence of metabolic (i.e., insulin resistance) and endocrine (i.e., PPID) abnormalities associated with heightened risk, special management is required for prevention of further episodes of pasture-associated laminitis. Lowering the risk of laminitis involves two primary components: 1) alleviation of insulin resistance and hyperinsulinemia, and 2) restricted access to feedstuffs (especially high NSC pasture) that may precipitate development of laminitis in these susceptible animals.

The two most important interventions in the management of obese, insulin resistant horses and ponies are dietary restriction and increased physical activity. Both will promote weight loss and therefore improvement in insulin sensitivity, while exercise can improve insulin sensitivity independent of its effect on body weight and fat mass. In some situations, the administration of levothyroxine sodium is indicated to accelerate weight loss and improvement in insulin sensitivity, for example when dietary restriction and increased exercise fail to control the laminitis. The reader is referred elsewhere in this guide (Chapter 5) for a detailed discussion on medical management of EMS horses. The remainder of this section focuses on strategies for limiting intake of NSC from pasture (and other feedstuffs) by equids at high-risk for pasture laminitis.

Analysis of forage and feed carbohydrates

Plants contain both structural (cell wall constituents, including cellulose, hemicellulose, lingo-cellulose and lignin) and nonstructural (NSC) carbohydrates. The NSC fraction includes simple sugars (monosaccharides, disaccharides), starches, oligosaccharides (including fructans), and soluble fibers (gums, mucilages and pectins). Much of the discussion on forage carbohydrates and laminitis risk has focused on fructans but other components of NSC, especially the simple sugars and starches, also may be important. Therefore, an ideal forage analysis system would provide an accurate breakdown of all NSC components. Commercial forage testing laboratories utilize a number of different analytical techniques and terminologies to describe the different carbohydrate fractions, leading to some confusion in the equine community. For example, NSC has been defined three ways:

1. **NSC by difference** according to the following equation using values from proximate nutrient analysis:
   NSC = 100 - (crude protein percent + nutrient detergent fiber percent + moisture percent + fat percent + ash percent)
   This NSC value represents sugars, starch, fructans, but also includes certain pectins, gums, mucilages.

2. **NSC by analysis where NSC** = water soluble carbohydrates (WSC) + starch (measured by enzymatic assay).

3. **NSC by analysis where NSC** = ethanol soluble carbohydrates (ESC) + starch (enzymatic assay). This definition was recently adopted by the Dairy One Forage Laboratory.

The WSC fraction includes simple sugars (e.g., glucose, sucrose, fructose) and oligofructoses (i.e., fructans), whereas ESC is an estimate of simple sugars only. Techniques are available for direct measurement of fructans in forage samples (e.g., chromatography), but as yet these methods have not been adopted by commercial laboratories. Fructans can be estimated by subtracting ESC from WSC but it should be understood that this is only a rough estimate because some fructans (especially the shorter chain oligofructoses) may be soluble in ethanol, i.e., included in the ESC fraction.

Some owners and farm managers have used periodic assessments of pasture NSC to determine the periods of highest risk when susceptible animals should have restricted or no access to pasture. In addition, measurement of carbohydrates in hay and other feedstuffs is recommended for selection of feeds suitable for laminitis-prone horses and ponies. This author prefers to measure WSC, ESC and starch in forage and feed samples. These data provide information on the glycemic and insulinemic potential of the forage or feed (i.e., ESC and starches) as well as the potential for the feed to be subject to rapid fermentation, all of which is relevant to the feeding management of insulin resistant, laminitis-prone horses and ponies.

Decisions on pasture turnout and strategies to limit intake of nonstructural carbohydrates

As pasture-associated laminitis occurs at pasture, the most obvious way to avoid the condition is to prevent access to pasture and to feed forage alternatives that are low in the carbohydrates known to be involved in triggering the disease. However, complete elimination of pasture access is not always necessary and many horses or ponies that have had one or more episodes of pasture laminitis can return to grazing activity providing there has been successful implementation of countermeasures to obesity and IR. Decisions regarding whether and to what extent affected animals can be allowed access to pasture must be made on a case-by-case basis, but in general:

- The horse or pony should be held off pasture until there has been complete resolution of the acute laminitis episode and, where indicated, diagnostic testing for IR and PPID. If there is no evidence of EMS or PPID, a gradual re-introduction to pasture may be considered. Start with one to two hours of grazing, once or twice per day, or turnout for longer periods if the horse is fitted with a grazing muzzle. More caution may be required when the pasture is green and growing rapidly (e.g., in spring).

- Obese, IR horses should be held off pasture for a longer period (e.g., two to three months), allowing time for implementation of management changes (i.e., dietary restriction, increased physical activity) that result in improved insulin sensitivity. *Even then, it is advisable to severely restrict or avoid any grazing during periods in which the pasture forage NSC content is likely to be high, e.g., spring and early summer; after summer and fall rains that cause the grass to turn green; and pastures that have been frosted or drought stressed (both can result in fructan accumulation).*

- Some IR horses and ponies with history of repeated episodes of laminitis require permanent housing in a dry lot because they appear to be susceptible to further episodes of laminitis in the face of even small variations in pasture availability and nutrient content.

Although restricting grazing to one to two hours at a time seems a reasonable strategy to limit NSC intake, in reality there is minimal information on the quantity of pasture a horse or pony may be able to ingest during these short periods of grazing activity. One preliminary study[15] indicated that ponies may ingest up to 40 percent of their typical daily DM intake as grass during three hours of turnout. Therefore, restricted grazing may not adequately limit daily intake of NSC and rapidly fermentable carbohydrates, particularly at times of the year when pasture forage sugar and/or fructan content is high.

As mentioned, on sunny days NSC content tends to rise during the morning, reaching maxima in the afternoon and declining overnight. In one study of spring pasture in northern Virginia,[23] the nadir in forage NSC occurred between 0400 h and 0500 h (approximately 15 percent NSC, DM basis), with highest values between 1600 h and 1700 h (approximately 22 to 24 percent NSC). Furthermore, serum insulin concentrations in mares grazing upon this pasture displayed a similar

circadian pattern that was strongly related to the NSC content. These observations support the common recommendation to turn susceptible animals out very late at night or very early in the morning with removal from pasture by mid-morning. Again, this approach may not be foolproof in spring because the NSC content of early morning pasture, while lower when compared to the same pasture in the afternoon, may not be safe for susceptible animals.

The following points summarize current advice regarding strategies for avoiding high NSC intakes by horses and ponies at risk for pasture laminitis:

- Animals predisposed to laminitis should be denied access to grass pastures during the growing season.
- At other times of the year, limit the amount of turnout time each day (e.g., one to three hours) and turn animals out very late at night or very early in the morning removing them from pasture by mid-morning at the latest (as NSC levels are likely to be at their lowest late at night through early morning).
- Alternatively, limit the size of the available pasture by use of temporary fencing to create small paddocks, or use a grazing muzzle.
- Avoid pastures that have not been properly managed by regular grazing or cutting as mature stemmy grasses may contain more fructan (it is stored in the stem).
- Do not turn horses out onto pasture that has been exposed to low temperatures in conjunction with bright sunlight, such as occurs in the fall after a flush of growth; or on bright, cool winter days as cold temperatures will reduce grass growth resulting in the accumulation of fructan.
- Do not allow animals to graze on recently cut stubble, as fructan is stored predominantly in the stem.

Alternative feeds

Animals denied access to pasture for most or all of the day will require provision of alternative feedstuffs. Horses at maintenance require approximately 2.0 percent of their body weight as forage or forage plus supplement to meet daily nutrient requirements. Grain and sweet feeds should not be fed and the feeding of other "treats" such as carrots and apples should be discouraged. Forage (as hay or hay substitute such as chop, chaff or haylage) should be the primary, if not sole energy providing component of the ration. Mature grass hay (i.e., with visible seed heads and a high stem-to-leaf ratio) has higher fiber and lower NSC when compared to immature hay, and is suitable forage for the obese horse or pony. Alfalfa hay or other legumes such as clover is less preferred because, on average, these forages have higher energy and NSC content when compared to grass hay. A NSC content of less than 10 to 12 percent is recommended. Alternatively, the water-soluble carbohydrate content (sugars and fructans) can be substantially reduced by soaking in clean water for 20 to 30 minutes prior to feeding. Caution is required when feeding significant amounts of poorly digestible, highly silicated forages; anecdotally, this practice increases the risk of impaction colic in some animals. Ensiled forages generally have lower NSC contents than hay made from the same crop. However, despite the generally lower NSC content of haylage compared to hay, the high palatability of some haylages may result in higher total NSC intake. Ideally, the results of proximate nutrient analysis, including direct measurement of starch, sugars and fructans (i.e., NSC), should be reviewed before selection of the hay.

Forage only diets will not provide adequate protein, minerals or vitamins. Therefore, we recommend 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, copper, zinc, selenium and other minerals typically found in mature grass hays. These products are often designed to be fed in small quantities (e.g., 0.5 to 1.0 kg per day); they can be mixed with chaff (hay chop) to increase the size of the meal and extend feeding time, which may alleviate boredom in animals provided a restricted diet. In some areas, forage-based, low calorie feeds complete with vitamins and minerals are available commercially; this type of feed offers convenience and may be used as a substitute to hay or fed as a component of the ration along with hay.

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CHAPTER 8

Management of Chronic Laminitis

Dr. Steve Adair

There are several phases of laminitis; these include the developmental, acute, subacute, and chronic phase. This chapter will deal with the diagnosis and management of horses that suffer from chronic laminitis. The onset of chronic laminitis begins when there is evidence of structural or morphologic change within the hoof capsule. During this stage, the foot will begin to fail mechanically. This mechanical failure may appear in as little as 24 hours after the onset of clinical signs or may take days to weeks to become apparent. Chronic laminitis may be further characterized as chronic stable or chronic unstable laminitis. Chronic stable laminitis is evidenced by a stable coffin bone with the hoof wall and sole growing and a steady clinical improvement. Chronic unstable laminitis is characterized by continued clinical deterioration or recurrence of pain after a period of improvement.

Treatment of chronic laminitis requires a commitment from the veterinarian, farrier, and owner. It is important to set realistic goals and outcome measures. The veterinarian should have a clear understanding of what the owner wants out of the horse, and at the same time the veterinarian should clearly convey the prognosis and expense involved. Euthanasia is an option.

Management

A thorough history and physical exam is important. There should be a detailed examination of each hoof that includes digital palpation and hoof testing. It is very important to obtain quality lateral and dorsopalmar/plantar (DP) radiographs at the initial presentation and sequentially during the healing process. Lateral radiographs allow one to determine the degree of rotation, amount of sinking, sole depth, and dorsal hoof wall thickness. The DP radiographs are used to determine medial or lateral sinking. Medial sinking most commonly occurs in the forefeet, while lateral sinking primarily occurs in the hindfeet **(Figure 8.1)**. These radiographs should have strategically placed radiopaque markers so that the coronary band, sole surface, dorsal hoof wall surface, and apex of frog can be identified. If measurements are going to be made from the radiographs, one marker should be of known length so that errors due to magnification can be corrected. The markers should be placed in a consistent location so that they may be placed in the same location on subsequent radiographs **(Figure 8.2)**. This is important when trying to determine sinking of the digit within the hoof

capsule. Venograms may also be indicated upon initial presentation as well as at selected time intervals during treatment **(Figure 8.3 A and B)**. Properly obtained venograms can demonstrate areas of compromised circulation such as the coronary plexus or the circumflex vasculature. Caution is indicated when using venograms prognostically. They are subjective in interpretation and, unless properly performed, artifacts leading to misinterpretation may be introduced. Some filling defects will be eliminated once the biomechanics of the digit have been improved.

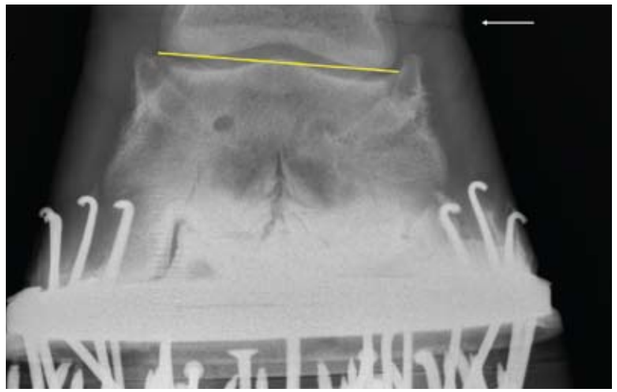

Figure 8.1 DP radiograph demonstrating medial sinking (white arrow). Note abnormal angle of pastern joint (yellow line)

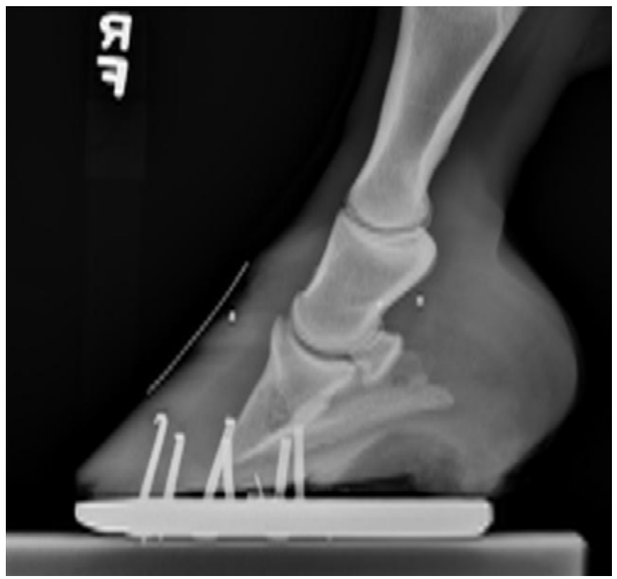

Figure 8.2 Lateral radiograph demonstrating marker placement

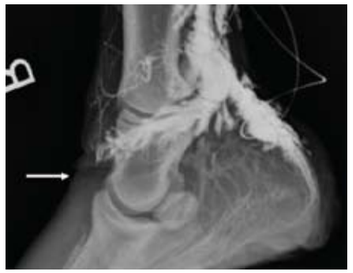

Figure 8.3A Lateral venogram. Note decreased filling in proximodorsal laminar region (white arrow)

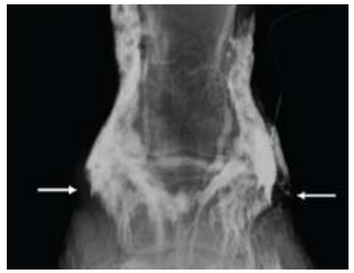

Figure 8.3B DP venogram. Note lack of filling of medial and lateral laminar regions (white arrows)

Management goals include providing mechanical support of the digit, normalizing the anatomy of the digit, pain relief, treating secondary complications, and management of diet, housing, and pasture. When presented with chronic stable laminitis, the most important management factors include normalization of the anatomy and management of diet, housing, and pasture. Many of these cases are reasonably comfortable and the most common complication is hoof abscessation. The abscessation is usually due to abnormal laminae; however, sequestration of the marginal border of the third phalanx will also cause abscesses to develop. In chronic unstable laminitis, mechanical support of the digit and pain relief are the primary goals.

Mechanical support and normalization of anatomy

With chronic stable laminitis, the goal of therapy is realignment of the coffin bone, moving the break over point back, providing good heel support, and improving sole depth. In order to realign the coffin bone, heel must be taken off. The amount of heel to be removed can be determined from a lateral radiograph.

In the case of chronic unstable laminitis, mechanical support of the bony column is critical. No attempts to change the biomechanics of the hoof should be attempted until the bone has stabilized for seven to ten days. The goal of mechanical support at this stage is to prevent additional laminar damage. Stall confinement is imperative at this time. Ambulation will cause additional tearing of the laminae. The load should be transferred away from diseased laminae. Shoes concentrate the forces around the periphery of the hoof, thus they can contribute to tearing and shearing of the laminae. If at all possible, the shoes should be removed and replaced with sole supports. Shoe removal may be accomplished safely by rasping the clinches and pulling one nail at a time.

Sole support is an important therapy that aids in transferring the load away from the hoof wall, thus protecting the laminae. It may be provided by

a number of means. There are several different types that can be used, depending on the case. The most economical is the use of one- to two-inch high density STYROFOAM™ (The Dow Chemical Company). It is cut to the shape of the bottom of the hoof and taped into place. The horse is allowed to stand with the Styrofoam in place for a few hours so that it conforms to the bottom of the foot. It is then removed and the toe portion in front of the apex of the frog is removed. The remaining portion is replaced onto the foot and a second one- to two-inch piece is taped over it **(Figure 8.4)**. The resulting application relieves pressure at the toe and also mildly elevates the heels to relieve the pull of the deep digital flexor tendon. A second method involves the placement of soft sole putty (Advance Cushion Support, Nanric, Inc., Versailles, Kentucky) in the caudal two-thirds of the sole. It should be level to slightly below the ground surface of the hoof wall once it has set **(Figure 8.5)**. It is then held in place with Elastikon®. A third method involves the use of Soft-Ride® boots (Soft-Ride, Inc., Vermilion, Ohio). These boots come with five different orthotic inserts including dual density inserts that provide soft cushioning cranial to the apex of the frog but firmer support for the caudal two-thirds of the foot **(Figure 8.6)**. The last method is used with sinkers. Soft sole putty is applied to the bottom of the foot so that it extends below the hoof wall **(Figure 8.7 A and B)**. It is higher in the center of the foot and thins out and stops as it approaches the wall. It is allowed to set and held in place with VetWrap®. The horse is then allowed to bear weight to check for comfort level. The center thickness may have to be adjusted depending on the comfort of the horse. The goal is to remove as much weight bearing on the wall as possible. The foot is then placed into a foot cast that ends in the pastern region **(Figure 8.8)**. One other option is the use of sole putty coupled with the Redden Ultimate Wedge (Nanric, Inc., Versailles, Kentucky).

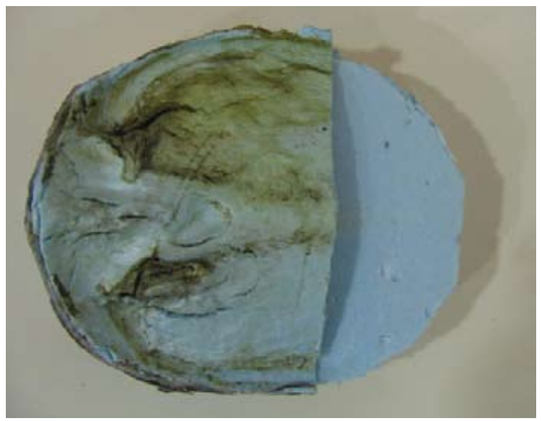

Figure 8.4 High density Styrofoam sole support.

Figure 8.5 Soft sole putty in caudal two-thirds of sole.

Figure 8.6 Soft-Ride® boot with dual density insert.

Figures 8.7 A and B Soft sole putty application used with sinkers.

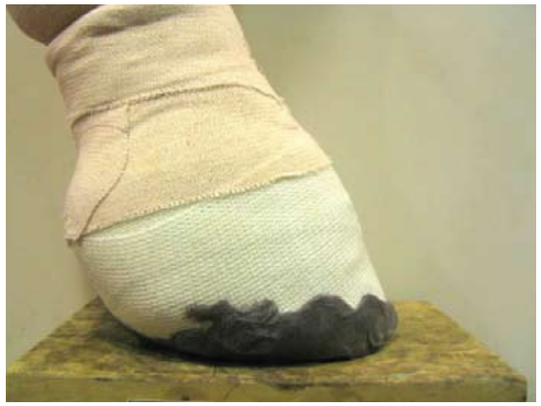

Figure 8.8 Foot cast used with sinkers.

Compression of the coronary band and vascular plexus can also be a problem. This is evident by filling defects in the coronary band region on the venogram or deviation of the rings in the hoof towards the coronary band **(Figure 8.9)**. In these instances, coronary grooving may be indicated **(Figure 8.10)**. The goal of grooving is to decrease compression of the coronary band and vasculature by the hoof wall. A one-half inch groove is cut into the hoof wall approximately one-half inch distal to the coronary band. The depth of the groove is just superficial to the junction of the dermal and epidermal laminae. The length of the groove should cover the length of the involved segment. In the case of a medial sinker this would be the length of the medial quarter. This procedure will allow the hoof wall to grow normally from the coronary band. It can be repeated if necessary as the hoof wall grows.

If rotation continues despite providing adequate support and improving biomechanics, a deep digital flexor tenotomy may be considered. The goal of this procedure is to decrease the pull of the deep digital flexor tendon on the coffin bone. It is most commonly performed in the mid-cannon region of the standing horse **(Figure 8.11)**, though it can be performed in the mid-pastern region also. Prior to transecting the tendon, an extended heel shoe should be placed to provide support and prevent the toe from coming off the ground. This procedure often provides significant pain relief and can be repeated if necessary. This procedure is often considered a "last ditch effort"; however, if done early in the disease process, the horse may return to previous function. The prognosis is much worse for return to function if it is performed late in the disease process.

The overall goal of the normalization of the anatomy is to return the coffin bone to its normal position within the hoof capsule. In the case of a horse that rotates, this

means that the heels will need to be lowered and the dorsal hoof wall will have to grow parallel with the dorsal aspect of the hoof wall. In the case of a sinker, the coffin bone sits in fairly normal position (i.e., minimal to no rotation), and one relies on support of the bony column while a new hoof wall grows.

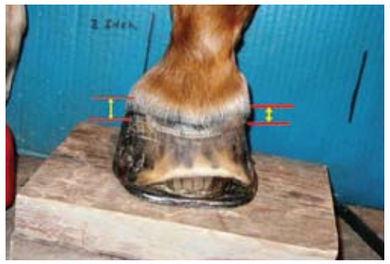

Figure 8.9 Horse with lateral compression of coronary band.

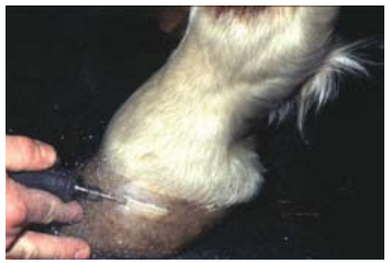

Figure 8.10 Coronary grooving.

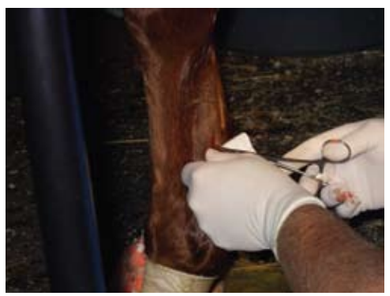

Figure 8.11 Deep digital flexor tenotomy in mid cannon region.

Derotation trimming and shoeing can only be done under radiographic guidance. Good lateral radiographs are essential. Using the lateral radiograph, a line is drawn parallel to the dorsum of the coffin bone. This line should be 15 to 20 mm away from the coffin bone and will represent the line of the new dorsal hoof wall **(Figure 8.12, Line A)**. A second line is drawn parallel to and 15 mm away from the solar surface of the coffin bone **(Figure 8.12, Line B)**. This will represent the

new weight–bearing surface of the foot. It is important to realize that the location of this line will be dependent on sole thickness. You will not be able to take off as much heel if sole depth is very shallow. The point of break over is determined by dropping a line from the tip of the coffin bone to the ground **(Figure 8.12, Line C)**. As an alternative, the point of break over can be moved even further caudally to lie under the extensor process **(Figure 8.13)**. After this, the toe should be backed up as much as possible. In many instances, when the shoe is placed, there will be no contact between it and the foot cranial to the point of break over. Once shoeing is complete, this area can be filled with soft polyurethane, being careful not to put pressure on the sole. Trimming and shoeing in this manner increases the tension on the deep digital flexor tendon. This may increase pain and, to counteract this, axially placed wedges are often applied to the ground surface of the shoe. There are commercially available shoes (EDSS Inc., Penrose, Colorado) that accomplish this or as an alternative wedge rails can be fashioned with acrylic. As the horse becomes more comfortable, the height of the wedges should be decreased. The overall goal of this technique is to move the point of break over caudally, give good caudal heel support, and to align the weight bearing surface of the coffin bone to the shoe. When this is properly performed, the biomechanics of the foot are more normal, compression of the coronary band in the dorsum of the hoof is reduced, and pressure is taken off the sole cranial to the apex of the frog. Depending on the rate of hoof growth, this procedure will need to be repeated at three to four week intervals. As time progresses, the shoeing interval can be lengthened to five weeks. Ultimately, the goal would be to obtain normal coffin bone position and a sole depth of at least 15 mm. At this time the horse may be able to return to work or allowed to go barefoot.

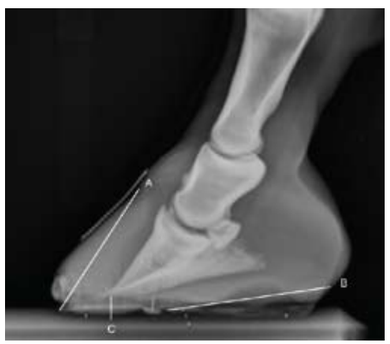

Figure 8.12 Derotation trimming. Amount of toe to be removed (line A); amount of heel to be removed (line B); point of break over (line C).

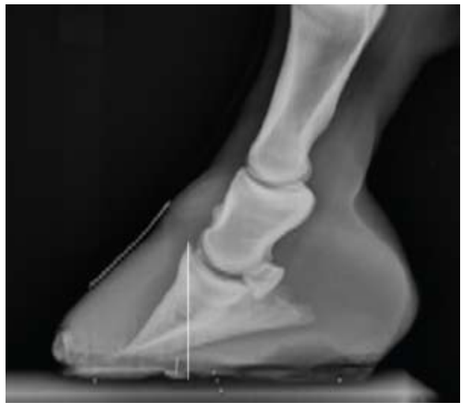

Figure 8.13 Alternative break over point (white line).

Dorsal hoof wall resection and abscesses

It is very common for abscesses to develop at the toe and migrate up the white line to break out at the coronary band **(Figure 8.14)**. In these cases, the toe and dorsal hoof wall will need to be removed for drainage. If at all possible a complete dorsal hoof wall resection should be avoided. To prevent excessive movement of the medial and lateral hoof, a bridge of hoof wall can be maintained across the center of the dorsum of the toe. This allows for treatment of the abscesses while maintaining stability.

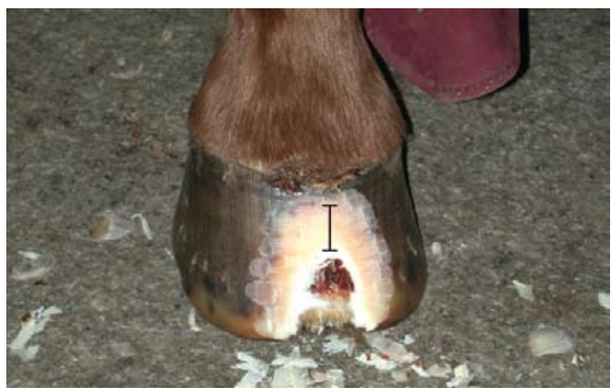

Figure 8.14 Hoof wall resection. Black line with bars indicates the amount of hoof wall to be left.

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APPENDIX 1

Endocrine Monitoring Form

Preparation for our visit:

1. Please schedule an appointment for before 10:00 AM and plan for us to perform endocrine testing before any other procedures.
2. Keep your horse in a stall or dirt paddock the night before our visit and do not feed any grain. Leave your horse with one flake of hay after 10:00 PM the night before and try not to provide any feed the morning of testing. If your horse becomes stressed when feed is withheld, provide one or two flakes of hay. Try to minimize stress.

Date _____

Patient _____

1. Owner's assessment of body condition and neck crest

   _____

   _____

2. Any laminitis episodes in last six months? _____
3. Any changes in haircoat or shedding? _____
4. Other medical history _____

   _____

   _____

Record current housing (approximate time spent in stall/paddock/pasture)

_____

Record current diet (including approximate amounts fed)

_____

Record current exercise regimen

_____

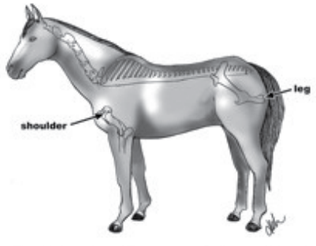
Recommended testing

Insulin Resistance (IR)	PPID (Equine Cushing's Disease)
☐ Resting insulin and glucose levels ☐ Combined glucose-insulin test (CGIT)	☐ Resting ACTH level ☐ Oral domperidone challenge test ☐ Dexamethasone suppression test

APPENDIX 2

Physical Measurements Form

Dr. Nicholas Frank



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Date _____

Patient _____

Veterinarian _____

Body weight _____ pounds/kg

Body condition score _____ (1 to 9)*

Height at withers _____ inches/cm

Girth circumference _____ inches/cm

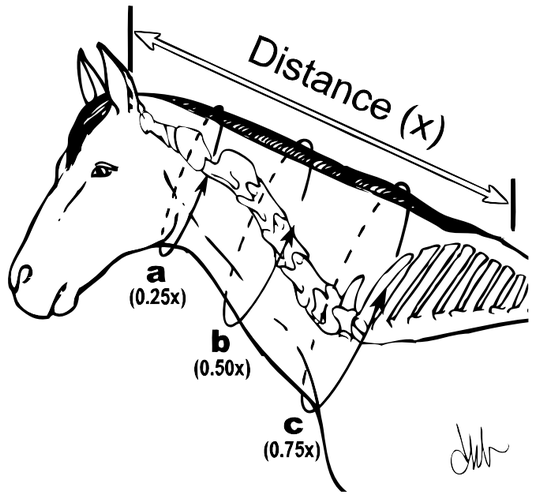
Length _____ inches/cm (point of shoulder to pin bone)

Distance (x) from poll to withers with head in normal position _____ inches/cm

A. Circumference of neck is _____ inches/cm at 0.25x

B. Circumference of neck is _____ inches/cm at 0.50x

C. Circumference of neck is _____ inches/cm at 0.75x



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*Refer to body condition chart (include a body condition chart)

APPENDIX 3

Oral Domperidone Test

Dr. Nicholas Frank

Testing procedure

This is a new test for ***pituitary pars intermedia dysfunction*** (PPID; also called ***equine Cushing's disease***) that was developed by researchers at Purdue University.[60] Domperidone is a D_2 dopamine receptor antagonist used for the treatment of agalactia in mares that have been exposed to endophyte on fescue grass (fescue toxicity). This drug is available in a gel form that is packaged in a dose syringe (Equidone®, Equi-Tox Inc., Central, South Carolina) for oral administration, and it costs approximately $50 per tube.

Sample handling

This test involves the measurement of plasma ACTH concentrations, so special sample handling is required.

Sampling conditions: Plastic tubes containing EDTA must be used and samples should be centrifuged within two hours of collection. Samples should be kept standing (to allow separation) in a rack inside a refrigerator or cooler with ice packs. Veterinarians in ambulatory practice should consider enlisting the help of the horse owner to transport samples back to the office.

Storage and shipping conditions: A minimum of 1 mL plasma should be harvested from each blood sample and transferred to plastic storage tubes. Plasma samples must remain cool at all times when they are handled. *Samples should be sent via overnight mail the same day or frozen (-20° C) overnight and then shipped*. On the day of shipping, samples should be packaged in a cooler with ice packs and sent to the laboratory via courier or overnight mail. It is very important to include enough ice packs to ensure that samples remain cold at all times. Values obtained from plasma samples that have warmed above 4° C (refrigerator temperature) are likely to be inaccurate.

Laboratories that measure ACTH in equine plasma include:

Cornell University College of Veterinary Medicine Animal Health Diagnostic Center (www.diaglab.vet.cornell.edu); telephone: ph (607) 253-3900

Michigan State University Diagnostic Center for Population and Animal Health (www.animalhealth.msu.edu); ph (517) 353-1683

Procedure

1. Testing should begin in the morning between 8:00 AM and 10:00 AM.
2. The first blood sample is collected before domperidone is administered.
3. One tube of Equidone® containing 25 mL gel (2.75 grams domperidone in total) should be administered by mouth to a 500-kg horse. This is equivalent to 5.5 mg domperidone/kg body weight and the appropriate dose should be calculated for smaller horses and ponies. Each milliliter of gel contains 110 mg domperidone.
4. A second blood sample should be collected four hours later if testing is performed from January to August (middle and eastern United States) and samples should be collected two and four hours after domperidone is administered if testing is performed in the fall.

Principle of the test

Horses with PPID secrete ACTH from hyperplastic or neoplastic tissue within the pars intermedia of the pituitary gland. This region of the pituitary gland does not secrete ACTH in the healthy animal. The pars intermedia is under tonic inhibition from dopamine produced by dopaminergic neurons originating from the hypothalamus and terminating in this region of the pituitary gland. Domperidone is a D_2 receptor blocker, so administration of this drug blocks inhibition by dopamine, which allows increased activity within the pars intermedia. This increase in activity causes more ACTH to be secreted into circulation when PPID is present. Plasma ACTH concentrations significantly increase after domperidone administration if the horse or pony suffers from PPID.

One confusing aspect of this test is that PPID results from degeneration of dopaminergic neurons, yet this test is based upon domperidone blocking the actions of dopamine produced by these neurons. It must therefore be recognized that dopaminergic neurons may be reduced in number in horses with PPID, but dopamine is still being secreted. Domperidone blocks the inhibitory actions of dopamine, which allows activity within the pars intermedia to increase. In horses with PPID, abnormal melanotropes within the pars intermedia are secreting ACTH and they produce more of this hormone after domperidone is administered.

Interpretation

1. A twofold or higher increase in plasma ACTH concentration after four hours is a positive result for PPID between January and August. The ACTH response to domperidone is exaggerated in the autumn, so a greater than twofold increase at two hours is a positive result between September and December. A horse that shows a less than twofold increase at two hours in the fall, but a positive result at four hours should be retested.
2. An elevated pre-domperidone (baseline) ACTH concentration is indicative of PPID and a cut-off value of 45 pg/mL (10 pmol/L) is generally used. Plasma ACTH concentrations are reported in pg/mL or pmol/L. Values reported in pg/mL can be converted to pmol/L using a multiplication factor of 0.22.
3. The ODT can be modified by instructing the horse owner to administer the domperidone four hours prior to the appointment time (two hours prior when testing is performed in the fall). When this single-sample approach is used, a plasma ACTH concentration greater than 100 pg/mL (22 pmol/L) is considered positive for PPID (personal communication; Dr. Janice Sojka; April 2008).

REFERENCES

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APPENDIX 4

Combined Glucose-Insulin Test

Dr. Nicholas Frank

Preparations

Do not feed any grain or other concentrates for at least six hours prior to testing, but hay should be fed to keep the horse calm.

Insert the intravenous (IV) catheter without stressing the horse (ideally place it the night before). Prepare the dextrose and insulin syringes. Fill a 3 mL syringe with 1.5 mL sterile physiological (0.9 percent) saline. Draw the insulin into a tuberculin syringe and then inject it into the saline to give an approximately 2 mL volume.

You must purchase a hand-held glucometer and test strips from a drug store. We use the Medisense Precision QID model that costs approximately $65, but a more accurate AlphaTRAK® (Abbott Laboratories, Inc.) glucometer is now available for veterinary use. The start-up kit for this glucometer costs approximately $180.

Procedure

Draw a baseline (pre-injection) blood sample (10 mL). Fill one red-top (no anti-coagulant) tube for a serum insulin concentration and use the rest of the blood for a glucose measurement using the glucometer. You will collect two blood samples for insulin measurements: 0 and 45 minutes.

Infuse 50 percent (500 mg/mL) dextrose solution at a dosage of 150 mg/kg bwt, immediately followed by the regular insulin (Humulin R®, Eli Lilly, Inc.) at a dosage of 0.10 U/kg bwt.

Flush the catheter with 10 mL heparinized saline and then collect blood by drawing off and discarding 3 mL blood, taking the 2 mL sample, and then flushing with 5 mL heparinized saline. We use an extension set. Run whole blood on the hand-held glucometer and record blood glucose concentrations.

At 45 minutes, collect 10 mL blood and fill a red-top tube for your second insulin measurement. Use the rest of the blood for a glucose measurement.

Warning

Keep two 60 mL syringes of 50 percent dextrose on hand and infuse if the blood glucose is less than 40 mg/dL or if there are clinical signs of hypoglycemia (fasciculations, sweating, or weakness).

Insulin concentrations

Centrifuge the two red-top tubes and send the serum samples to the laboratory for insulin measurements.

Interpretation

The glucose response is the time taken for blood glucose concentrations to fall back below the baseline (pre-injection) level. Healthy horses are back below baseline in less than 45 minutes. You can stop the test after 45 minutes if a normal response has been detected.

The insulin response is the concentration at 45 minutes. In our laboratory, healthy horses have serum insulin concentrations less than 30 µU/mL at baseline and do not exceed 100 µU/mL at 45 minutes. Divide concentrations in pmol/L by seven to convert to units.

Combined Glucose-Insulin Test (CGIT)

Date _____ Horse ID _____ Weight _____ kg

Dextrose = _____ mL (150 mL of 500 mg/mL dextrose to a 500-kg horse)
Insulin = _____ mL (0.50 mL of 100 U/mL regular insulin to a 500-kg horse)

TIME OF DAY	INITIALS	TIME OF DAY	INITIALS
0 min _____ (Pre) Collect blood for insulin	_____	60 min _____	_____
5 min _____	_____	75 min _____	_____
15 min _____	_____	90 min _____	_____
25 min _____	_____	105 min _____	_____
35 min _____	_____	120 min _____	_____
45 min _____ Collect blood for insulin	_____	135 min _____	_____
		150 min _____	_____

APPENDIX 5

Client Information Sheet: Managing Insulin Resistance in Horses

Dr. Nicholas Frank

Horses, ponies, or donkeys can develop ***insulin resistance*** (IR) and this problem is important because insulin-resistant animals are more susceptible to laminitis (founder). Insulin resistance affects blood sugar regulation and is similar to type 2 diabetes mellitus in people. However, IR is milder than diabetes and problems may only be recognized after the condition has been present for several years (chronic IR). Unfortunately, we usually fail to recognize IR until after laminitis has developed.

Understanding insulin resistance

Insulin is a hormone produced by the pancreas that stimulates movement of glucose into insulin-sensitive tissues. These tissues become less responsive when IR develops, which slows the rate of glucose uptake unless additional insulin is secreted. The pancreas therefore responds to this problem by secreting more insulin, which means that higher insulin levels are detected in the blood (hyperinsulinemia) of most insulin-resistant horses and ponies. Insulin resistance leads to type 2 diabetes mellitus in humans, and this occasionally occurs in horses. Obesity and IR are related because fat accumulates within cells and interferes with insulin signaling.

Insulin resistance and laminitis

Insulin resistance may increase the risk of laminitis by compromising blood flow to hoof tissues. Insulin normally keeps blood vessels open, so insulin-resistant horses may have difficulty maintaining adequate blood flow to the feet, particularly when this system is challenged. Laminitis may be triggered when alterations in blood flow interfere with nutrient delivery to hoof cells.

Laminitis is usually triggered by changes in diet such as grain overload or grazing on pasture grass that is rich in starch or sugar (*pasture founder).* These dietary challenges are tolerated by healthy horses, but insulin-resistant horses may have more difficulty responding to these situations. Potential triggers for laminitis include 1) insulin resistance suddenly getting worse after grazing on pasture, 2) intestinal upsets caused by changes in diet that lead to transient systemic illness and altered blood flow, or 3) a combination of both.

Terminology

Insulin resistance is important because it predisposes horses to laminitis. Once IR has been detected, the cause of this problem must be investigated. If the horse is old (more than 20 years of age), it may suffer ***pituitary pars intermedia dysfunction*** (PPID), which is also called ***equine Cushing's disease***. Some horses with this hormonal condition suffer from IR, whereas others have normal insulin sensitivity. If there is no evidence of PPID and the horse is young or middle-aged, then ***equine metabolic syndrome*** (EMS) should be considered. Equine metabolic syndrome is the name given to describe horses and ponies that suffer from a clinical syndrome involving obesity, IR, and laminitis. Horses and ponies first develop the physical characteristics of EMS when they are young or middle-aged, and affected animals are more susceptible to laminitis. Most EMS patients are obese, but IR can also be detected in leaner animals. We must therefore divide patients into obese-EMS and lean-EMS categories. It is necessary to follow one management plan for obese insulin-resistant horses and another for lean horses with the same problem.

Insulin resistance and obesity

Horses that are too fat (obese) are more likely to suffer from IR, so it is better to maintain horses in a leaner body condition. As a rule of thumb, you should always be able to feel your horse's ribs as you run your hand across the chest. It is important to recognize that obesity and IR often occur together, but not all fat horses are insulin-resistant and IR can develop in thinner animals. This emphasizes the importance of regularly screening for IR, particularly if your horse is overweight.

Many horses are overweight because they have a very efficient metabolism, and this may be genetically determined. These horses are sometimes referred to as easy keepers because they require fewer calories to maintain body weight. The physical appearance of the horse can indicate a problem with IR. Horses with IR often have a thick neck crest filled with fat (cresty neck), fat pads near the tail, or fat accumulation within the sheath or mammary gland regions. This is referred to as *regional adiposity* and horses with these signs should always be tested for IR.

Monitoring insulin resistance

Before we discuss the management of IR it is first important to outline the methods used to diagnose and monitor this problem.

Resting glucose and insulin concentrations

This is the simplest method of diagnosing and monitoring IR. One or two tubes of blood are collected and sent to a laboratory for glucose and insulin measurements.

Insulin concentrations are high (hyperinsulinemia) if the horse suffers from IR, whereas glucose concentrations are usually within normal range. If blood glucose concentrations are above the reference range (hyperglycemia), it is an indication that the problem is more severe.

However, this testing can only be used properly if blood samples are collected under the appropriate conditions.

Sampling conditions

- Pain and stress raise insulin concentrations, so levels will always be elevated if active laminitis is present at the time of testing. Patients must therefore be given adequate time to recover from laminitis before they are tested, and should be kept calm the night before sampling.
- Resting insulin concentrations are higher after grain or grazing on grass that is rich in sugar. Horses should not be sampled when they are grazing on pasture and all grain should be withheld for at least 12 hours.
- Horses should be placed in a dirt paddock or stall overnight and should ideally be held off all feed for six hours prior to sampling. Leave your horse with only one flake of hay after 10:00 PM the night before, so that it will be finished by approximately 2:00 AM in the morning. Some horses become very agitated if they are deprived of feed, so they should be fed hay throughout the night to avoid stress.
- Sampling procedures should be standardized, so blood samples should be collected in the morning before 10:00 AM.
- Tranquilizers must never be given within 12 hours of blood collection because these drugs increase serum insulin concentrations.

Limitations

- Early or mild IR can remain undetected when this screening test is used because insulin levels fall within reference range. Your veterinarian may recommend a more advanced procedure called the combined glucose-insulin test (CGIT) if your horse looks as though it suffers from EMS, but IR cannot be confirmed by measuring resting glucose and insulin concentrations.
- Test results vary between laboratories because different assays and running conditions are used. It is therefore important to use the reference range for the laboratory.

Combined glucose-insulin test

The CGIT is used when EMS is strongly suspected on the basis of physical characteristics and the medical history, but resting glucose and insulin concentration are within reference ranges. When the CGIT is performed, glucose and insulin are infused through an intravenous catheter and then blood glucose concentrations are measured at specific time intervals. Serum insulin concentrations are also measured twice during the test.

Managing obese horses with insulin resistance

It is important to manage IR because this will reduce the risk of laminitis. The most effective way of improving insulin sensitivity in obese horses is to induce weight loss.

1. Do NOT feed grain at all. A handful of beet pulp (that does not contain molasses) or low-sugar pelleted feed can be given as a treat if necessary, but that is all. Do not feed apples, carrots, or sugar cubes. Sugar aggravates IR in your horse in the same way that it would a person with diabetes.

2. Exercise your horse as often as possible. Use a lunge line or ride your horse for at least 15 minutes as many days of the week as you can manage. Walking your horse on a lead rope will also help. Exercise helps to lower your horse's blood insulin levels by improving insulin sensitivity.

3. Horses with laminitis (founder) must be taken OFF PASTURE COMPLETELY until their feet have recovered and IR has been controlled. Horses should be kept in dirt paddocks so that they can exercise (once laminitis has resolved), but not eat grass.

4. Low-sugar hay should be selected for horses with IR. Hay samples can be submitted to the Equi-analytical, Inc. laboratory (1-877-819-4110) to determine the carbohydrate content. This costs approximately $35 for complete analysis (test 602) and $19 if only carbohydrates are measured (test 644). When you receive your results, you must calculate the non-structural carbohydrate (NSC) content of the hay. Non-structural carbohydrates are found within plant cells and include simple sugars, starches, and fructans. Sugars and starches are most likely to aggravate IR, so we calculate a NSC value that reflects these components. This is accomplished by adding the percentages of starch and ethanol-soluble carbohydrate (ESC) provided in the report. As-fed percentages should be used and you should try to feed hay that is less than 10 percent NSC. If the NSC content is between 10 and 12 percent, it can still be fed if the hay is soaked in cold water for 60 minutes to leach out sugars before feeding.

5. A weight loss diet is necessary if your horse is obese. This is sometimes accomplished by simply eliminating grain and pellets from the diet if these feeds are being fed. Pasture access must also be temporarily suspended because it represents an unregulated source of calories. Ideally, you should try to keep your horse in a dry lot because this permits exercise, which increases caloric demand. The amount of hay fed should also be reduced. An obese horse should initially be fed 2 percent of current body weight in hay, and then this amount is lowered to 1.5 percent of current body weight, and finally 1.5 percent of ideal body weight over four weeks. For example, if the ideal body weight for your horse is 1,000 pounds, you should reduce the amount of hay fed to 15 pounds per day until weight loss has been achieved. Use kitchen scales to weigh the hay or purchase a hanging scale at a feed store. Divide the total amount of hay into two to four feedings per day.

6. Your horse is at high risk for laminitis triggered by diet (grain founder or grass founder) for as long as he/she suffers from IR. It is therefore important to hold your horse off pasture until resting glucose and insulin concentrations have returned to normal.

   Even after glucose and insulin values have improved, your horse is still at high risk for laminitis. You should never give your horse sweet feed and always avoid turnout on pasture when the grass is turning green and growing fast. This growth occurs in the spring as the weather turns warmer and during the summer after heavy rain. Temperate pasture grasses also accumulate sugar when they are stressed by drought or the onset of winter. The insulin-resistant horse is therefore at greater risk for laminitis when the pasture grass is in one of these dynamic phases. Horses with a history of IR should be held off pasture or made to wear a grazing muzzle at these high-risk times of the year. The use of fertilizers on horse pastures also increases the likelihood of problems with IR and laminitis. If you are returning your horse to pasture after a period of time in a stall or dirt paddock, start with one hour twice daily and gradually increase grazing time over one to two weeks. It is better for your horse to be turned out for multiple short one-hour periods than a single longer time period.

   You can also limit grazing by selecting one of the following confinement options:

   Dirt paddock
   Small paddock (no larger than a tennis court)
   Corner of the pasture or strip of land enclosed with electric fence
   Round pen that can be set up in the pasture and moved every week

   Recent studies have shown that the NSC content of pasture grass varies by season and time of day. The lowest sugar levels are found at night and during the early morning hours, so these are the best times of the day for your horse to graze. However, the opposite is true when temperatures drop below freezing at night because grasses store sugar in response to this stress. You should therefore avoid turnout on nights when frost is expected.

7. Proper hoof care is also important to lower the risk of laminitis in insulin-resistant horses. Consult with an experienced farrier.

8. Your veterinarian may recommend medical treatment of obesity if your horse is not losing weight on the recommended diet. Levothyroxine sodium (e.g., Thyro-L®) can be prescribed to accelerate weight loss and improve insulin sensitivity. Consult with your veterinarian about using this drug. This supplement was prescribed in the past when we thought that overweight horses suffered from hypothyroidism. We no longer consider hypothyroidism to be the cause of obesity in horses, but levothyroxine sodium can be prescribed at a higher dosage for three to six months to accelerate weight loss in obese horses.

9. Provide your horse with a balanced vitamin and mineral supplement.

Managing leaner horses with insulin resistance

These horses do not need to lose weight, but careful attention must be paid to their diet. The above recommendations for hay selection and pasture turnout should be followed, and horses should be exercised as often as possible. Leaner horses may require additional calories to maintain body weight and this can be accomplished by feeding more hay. A commercial pelleted feed designed for insulin-resistant horses can also be fed if body weight cannot be maintained on hay alone. These products are labeled as "low-starch," "low-sugar," or "low-NSC" feeds and may be referred to as safe for horses with IR. However, this is a relative term and should be used with caution. Examples of specialty pelleted feeds (in random order) include Triple Crown Low Starch®, McCauley Bros. Alam®, and Purina WellSolve L/S®.

If specialty feeds are not available in your area or are too expensive, then sugar beet pulp is an alternative. This feed is primarily digested in the large intestine, so it increases body weight, but has a minimal impact upon blood glucose concentrations. Molasses-free beet pulp should be purchased and it is advisable to first wash the feed and then soak it before feeding to remove sugars and prevent choke.

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