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PATHOLOGY OF METABOLIC-RELATED CONDITIONS

FRANK M. ANDREWS AND NICHOLAS FRANK
The University of Tennessee, Knoxville, Tennessee

Equine Cushing's Disease (Pituitary Pars Intermedia Dysfunction [PPID])

INTRODUCTION

Equine Cushing's disease (ECD) or pituitary pars intermedia dysfunction (PPID) results from hypertrophy, hyperplasia, or a functional adenoma in the pars intermedia of the pituitary gland and is frequently recognized in older horses (Frank et al., 2006a). The pituitary produces excessive amounts of adrenocorticotropic hormone (ACTH), which results in an increased secretion of cortisol from the adrenal glands (hyperadrenocorticism). The intermediate lobe of the pituitary gland is located between the pars nervosa (posterior pituitary) and the pars distalis of the anterior pituitary gland and is the primary site of disease. ECD develops when pars intermedia cells become hyperplastic or neoplastic and biologically active. Neoplastic cells form microadenomas (<5 mm) or macroadenomas (>5 mm) that are commonly referred to as pituitary adenomas. Hormones and other products (MSH, beta-endorphins, ACTH) of these neoplastic cells are responsible for the clinical signs associated with ECD. Current diagnostic tests, the overnight dexamethasone suppression or endogenous ACTH tests, may produce false positive and false negative results, making diagnosis of ECD difficult (Schott, 2002).

CLINICAL SIGNS AND PRESENTATION

Equine Cushing's disease is commonly found in older horses and ponies, so it should always be considered when evaluating horses over 18 years of age. Younger horses also develop ECD, but currently available diagnostic tests may not be sensitive enough to detect early disease. In a recent study, we evaluated 17 horses with histopathologic evidence of ECD. The horses ranged in age from 9 to 33 years, with a median of 23 years (Frank et al., 2006a). Ponies appear to be more susceptible to ECD, but no other breed or sex predilections are recognized (Schott, 2002).

Clinical signs in horses with suspected ECD include lethargy, loss of appetite, pot-bellied appearance, laminitis, hirsutism, hyperhidrosis (excessive sweating),

polydipsia (excessive water drinking), polyuria (excessive urination), increased supraorbital fat pads, and dental and foot diseases. Laminitis is the most important clinical manifestation of ECD because it results in pain and suffering, and can lead to retirement or even euthanasia when chronic problems develop. Many horses first develop laminitis when grazing on pasture and the disease is triggered by an increase in pasture grass sugar content. Sugar concentrations rise dramatically when the grass grows rapidly in the spring and summer after heavy rainfall, or when it is preparing for winter dormancy in the fall. This alters the large intestinal flora, changes intestinal permeability, and leads to the release of triggering factors into the blood. Horses with ECD may be predisposed to laminitis because they have weaker hoof tissues or altered blood flow as a result of increased blood cortisol (Johnson et al., 2002). Some affected horses are also insulin resistant, which may further lower the laminitis threshold. These predisposing factors make horses or ponies with ECD more sensitive to alterations in pasture grass sugar content, and therefore more susceptible to pasture-associated laminitis.

Horses with ECD commonly have a long, curly haircoat (hirsutism) that does not shed out during the spring or summer months. Hirsutism is sometimes considered to be pathognomonic for ECD, but protein deficiency can also lead to haircoat abnormalities in older horses. Overt hirsutism only occurs with advanced disease but careful examination will sometimes reveal the presence of long hairs along the palmar or plantar aspects of the legs or patches of longer hair on the body. Clients should also be questioned about the exact time of year that their horse sheds its winter coat and how this compares to other horses on the farm. An early sign of ECD is delayed shedding of the winter haircoat.

There are some similarities between ECD and equine metabolic syndrome (EMS, see below) because fat deposits expand in the neck region, a condition commonly referred to as a "cresty neck." Fat pads may also develop close to the tailhead and in the supraorbital area (above the eyes). Since these are common to both ECD and EMS, it is sometimes challenging to differentiate between the two conditions. As a general rule of thumb, horses with ECD have a thinner body condition because they have lost muscle mass, whereas horses with EMS tend to exhibit generalized obesity.

Corticosteroids stimulate the conversion of muscle protein into energy through gluconeogenesis. Loss of epaxial (muscle over the back) muscle mass can often be detected in older horses, but this alteration is more pronounced in animals with ECD. A pot-bellied appearance may be seen in horses with advanced ECD as the abdominal musculature thins and weakens. Because of the increased cortisol in the blood, horses and ponies with advanced ECD are more susceptible to diseases such as sinusitis, tooth root infections, or sole abscesses. This finding is attributed to the immunosuppressive actions of corticosteroids.

Hyperhidrosis (excessive sweating) is sometimes detected in animals with ECD and will persist even after the haircoat has been clipped. Polydipsia and polyuria may accompany ECD, but these signs are hard to detect until the disease is advanced.

Clients should therefore be instructed to measure water consumption with the aim of detecting polydipsia. Lethargy is detected in some animals with ECD and clients sometimes report that their horse has become more tolerant of pain. These findings are attributed to the release of beta-endorphins from the diseased pituitary gland.

Older horses are more likely to develop ECD because the dopaminergic inhibition of the pituitary gland decreases with age. Dopaminergic neurons extend from the hypothalamus to the pituitary gland and carry dopamine, which is an inhibitory neurotransmitter. Dopamine inhibits the activity of pituitary tissues and decreases ACTH secretion. It may also prevent the development of hyperplastic cells that subsequently become neoplastic. Loss of dopaminergic neurons is a normal aging process, but degeneration may be accelerated in some horses, and these animals are likely to more susceptible to ECD. Oxidative damage may be responsible for the loss of dopaminergic neurons that occurs with age (McFarlane et al., 2005a; McFarlane et al., 2005b).

Other conditions have been described in horses with ECD and include osteoporosis, delayed wound healing, central nervous dysfunction, suspensory ligament breakdown, and persistent lactation and infertility.

DIAGNOSIS

Changes in routine blood work may include increased blood glucose concentration (>100 mg/dL) and/or changes in white blood cell count (mature neutrophilia with lymphopenia). These findings are attributed to the effects of corticosteroids on glucose metabolism (insulin resistance and enhanced gluconeogenesis) and circulating leukocytes (demargination of neutrophils).

RESTING ACTH, INSULIN, AND GLUCOSE CONCENTRATIONS

We routinely screen horses for ECD by measuring plasma ACTH concentrations, and we also measure glucose and insulin concentrations to indirectly assess glucose metabolism. Elevated ACTH concentrations indicate that the horse suffers from ECD, and hyperinsulinemia accompanies insulin resistance (IR) because insulin secretion from the pancreas increases to compensate for the change in insulin sensitivity. IR is a defining feature of EMS, but also occurs in some patients with ECD. This condition is relevant to the management of ECD patients because insulin-resistant horses and ponies are more susceptible to laminitis. It is therefore important to recognize IR and improve insulin sensitivity through dietary management, exercise, and drug interventions.

For ACTH measurements, we routinely send blood samples to the Diagnostic Center for Population and Animal Health (DCPAH) laboratory at Michigan State University. According to its reference range, ECD is suspected when the plasma ACTH concentration is above 7.5 pmol/L (35 pg/mL) and is diagnosed when the concentration

is above 10 pmol/L (45 pg/mL). Unfortunately, it has been our experience that ACTH concentrations are not a sensitive indicator of ECD in horses and ponies. Animals with advanced disease tend to have elevated plasma ACTH concentrations, but early disease can go undetected (McFarlane et al., 2005a). Detection of hyperinsulinemia serves as a screening test for IR, but this is complicated by the fact that reference ranges vary considerably between laboratories. For instance, the DCPAH defines hyperinsulinemia as >300 pmol/L (43 mU/L; multiply by 7 to convert units), whereas the upper limit of the reference range is 30 mU/L (210 pmol/L) at the University of Tennessee Endocrinology Laboratory. Since we are screening patients for IR, we use a narrower reference range for insulin and assume that a value >20 mU/L is suggestive of IR. High-normal (>100 mg/dL or 5 mmol/L; multiply by 18 to convert units) glucose concentrations can also be detected in horses with IR. Patients with hyperinsulinemia should have a combined glucose-insulin test (CGIT) performed to further assess insulin sensitivity and document the degree of IR (Eiler et al., 2005). More subtle alterations in insulin sensitivity can also be assessed in horses or ponies with lower (<20 mU/L) serum insulin concentrations by applying glucose and insulin values to normograms that predict insulin sensitivity and pancreatic function in horses and ponies (Kronfeld, 2006).

DIURNAL CORTISOL RHYTHM TEST

Taking a single serum cortisol concentration will not help in the diagnosis of ECD, because blood concentrations fluctuate rapidly from minute to minute. However, serum cortisol concentrations generally decrease throughout the day, so the cortisol level is usually >30% lower in the evening than it is in the morning (Dybdal et al., 1994). This is referred to as the diurnal cortisol rhythm, and it is assumed that this pattern is lost when horses develop ECD because ACTH is now being released from the pars intermedia, which is not under negative feedback control. We performed a small study in which we measured and compared serum cortisol concentrations in four healthy mares every 2 weeks for 8 weeks. Of the 20 pairs of samples evaluated, the diurnal difference was <30% on 4 occasions (20% false positive rate) in healthy mares, indicating that the test has a low specificity. We do not routinely use this test in our practice, but it may be a useful screening test. However, you should only consider the negative result to be significant. Detection of a normal rhythm (>30% difference between morning and evening) indicates that ECD is unlikely to be present, but horses with positive results must undergo further testing before a diagnosis is made.

The only way to definitively diagnose ECD is to identify neoplastic tissue within the pars intermedia of the pituitary gland at postmortem examination. At present, an antemortem diagnosis of ECD can be made by (1) observing hirsutism; (2) increased plasma ACTH concentration; or (3) getting a positive result when a dexamethasone suppression test or combined dexamethasone suppression/thyrotropin-releasing hormone (TRH) stimulation test is performed (Eiler et al., 2005).

In our recent study, we found the sensitivity and specificity of hirsutism to be 71% and 95%, respectively, and only one false positive was identified (Frank et al., 2006a). The specificity of hirsutism is high, but the sensitivity is low because only animals with advanced disease are affected. In our practice, detection of overt hirsutism (long, curly haircoat) in an older horse is sufficient to begin pergolide therapy. However, protein deficiency can result in haircoat changes, so this potential problem should be addressed by feeding a protein supplement if the diet is poor.

A dexamethasone suppression test is performed by collecting a pre-injection blood sample and then injecting 0.04 mg/kg (20 mg for a 500-kg horse) dexamethasone intravenously. A second blood sample is collected 24 hours later. In a healthy horse, the plasma cortisol concentration will remain suppressed for greater than 24 hours. The plasma cortisol concentration measured 24 hours post-injection should be <10 ng/mL (1.0 µg/dL) if the horse is responding normally. The test is therefore positive for ECD if the plasma cortisol concentration is above 10 ng/mL when blood collected 24 hours post-injection is analyzed. Plasma cortisol concentrations do not remain suppressed (i.e., they "escape") in horses with ECD because neoplastic cells within the pars intermedia are not under negative feedback control. The pars distalis responds to negative feedback, so ACTH production is suppressed, but pituitary adenoma cells continue to secrete ACTH, and this is enough to raise the cortisol level above 10 ng/mL (1 µg/ml) within 24 hours.

The combined dexamethasone suppression/thyrotropin-releasing hormone test was developed at the University of Tennessee and first described 11 years ago (Eiler et al., 1997). We recently evaluated the accuracy of the test and found that combining results of both the dexamethasone suppression and TRH stimulation components of the test increased its sensitivity (Frank et al., 2006a). The sensitivity values for the two components of the test were 65% and 41%, respectively, whereas the combined test had a sensitivity of 88%. The specificity (76%) was limited by the dexamethasone suppression component of the test. These sensitivity values suggest that the dexamethasone test will fail to identify 35% of horses with ECD when used alone, but only 12% of horses with disease will be missed when the combined test is used. Inclusion of the TRH stimulation test is easily accomplished in a referral hospital setting, but this test is more difficult to perform in the field. Thyrotropin-releasing hormone is commercially available from Phoenix Pharmaceuticals, Inc. (www.phoenixpeptide.com; 25 mg vial for $35) or a reagent grade product can be purchased from Sigma Chemical, Inc. To perform this component of the test, a pre-TRH blood sample should be collected 3 hours after injecting dexamethasone and 1 mg of TRH (total dose) is injected intravenously. A post-TRH blood sample must then be collected 30 minutes later. Plasma cortisol concentrations increase by <66% over 30 minutes in healthy horses, whereas a horse with ECD has a ≥66% increase over the same time period. Although corticotropin-releasing hormone (CRH) secreted by the hypothalamus is primarily responsible for the release of ACTH, some TRH receptors are present within tissues of the pars distalis and pars intermedia. The abundance of

these receptors is low in healthy pituitary tissue, so ACTH is not released in response to exogenous TRH. However, neoplastic tissues expand the size of the pars intermedia and have more TRH receptors, so they respond positively to the same challenge. Pituitary adenoma cells release more ACTH in response to TRH, which stimulates the release of cortisol. It is advantageous to administer dexamethasone 3 hours before TRH because it lowers the baseline plasma cortisol concentration and therefore makes it easier to recognize the post-injection peak.

The approach to horses suspected of having ECD involves the following steps:

(1) A horse or pony with hirsutism is assumed to suffer from ECD and pergolide therapy is initiated. Resting glucose and insulin concentrations are measured and a CGIT is ideally performed to assess insulin sensitivity, which is important for the management of laminitis.

(2) Detection of a plasma ACTH concentration above 10 pmol/L (between November and July) is diagnostic for ECD and pergolide is prescribed. Insulin sensitivity is also assessed.

(3) If there is a high suspicion of ECD, the potential risks of performing a dexamethasone suppression test are discussed with the client. Insulin sensitivity is also assessed prior to the dexamethasone suppression test because corticosteroids induce transient IR (Donaldson et al., 2005). If the client accepts the risks and there is an adequate veterinarian/client relationship, a combined dexamethasone suppression/TRH stimulation test is performed. If the client has reservations about the test, the horse's IR (if present) is managed and a 6-month trial of pergolide is prescribed.

(4) If a cresty neck is the only clinical sign detected, insulin sensitivity is assessed and the diagnosis of EMS is considered.

TREATMENT

Pergolide is the drug of choice for treating ECD. This drug increases the production of the inhibitory neurotransmitter dopamine, which has two potential effects: (1) it suppresses the activity of neoplastic pars intermedia cells, and (2) it inhibits growth of the tumor(s). This drug is administered orally at a dosage of 1 mg (total dose) per day, and the cost is approximately $2.00 per day. We usually recommend purchasing the drug through a reputable compounding pharmacy, but quality control is important and there have been anecdotal reports of compounded pergolide lacking efficacy. Side effects of pergolide seen in humans include anorexia, diarrhea, and depression, but horses generally tolerate the drug well. We have increased the dosage to 4 mg/day in some ECD patients with advanced disease. Some clients claim that they have seen a better response when pergolide is given twice daily, but this issue has not been studied. Other drugs that can be used to treat horses or ponies with ECD include cyproheptadine

(a serotonin antagonist) and trilostane (a 3ß-hydroxysteroid dehydrogenase competitive inhibitor), which is currently available only from Canada. Serotonin is an excitatory neurotransmitter, so cyproheptadine suppresses pituitary activity. Trilostane inhibits the rate-limiting step in cortisol synthesis within the adrenal gland and is administered orally at a dosage of 0.5 to 1.0 mg/kg. This drug is more commonly used in Europe, but pergolide still remains the drug of choice for treating ECD in horses and ponies. The adrenocorticolytic drug o,p'-DDD (Lysodren®) used to treat Cushing's disease in dogs is not effective in horses.

MANAGEMENT

Some horses with ECD also suffer from IR, so they should be placed on diets that contain less sugar. A diet composed primarily of hay is often recommended, but if concentrates must be fed to meet energy demands in exercising horses, they should be provided without exacerbating IR. You must therefore consider the following features: (1) the NSC content of the feed, (2) its glycemic index, and (3) the amount of feed provided. The glycemic index is the degree to which blood glucose concentrations increase after the feed is consumed (area under the postprandial blood glucose curve). Feeds with both a high NSC content and high glycemic index can exacerbate IR when fed in large quantities. Grazing on pasture presents the greatest risk to the horse with IR because the NSC content of pasture grass varies widely and fluctuates with changes in rainfall and temperature. Limited grazing time or use of a grazing muzzle should be considered when managing horses with IR, and some patients must be held off pasture altogether to prevent laminitis from being triggered.

ECD VS. EMS

This is a controversial question because there is still debate about the definition of equine metabolic syndrome (EMS) in horses, and some clinicians question whether the condition is simply an early manifestation of ECD. I do not think that EMS is caused by ECD, but the two conditions are related. Horses with EMS appear to be predisposed to ECD, and it develops at an earlier age in these animals. A horse can therefore transition from EMS to ECD as it ages. This transition tends to occur when the horse is between 10 and 20 years of age and it is recognized by a shift in body condition from generalized obesity to a thinner condition because of lost muscle mass. The cresty neck remains evident and fat pads close to the tailhead may become more prominent. Other changes can include the development of abnormal shedding patterns or the growth of longer hairs on the palmar and plantar aspects of the legs. Equine metabolic syndrome begins with a genetic difference that makes the individual horse require fewer calories to maintain body weight ("easy keeper"). Current feeding and management practices cause weight gain, and adipose tissues expand quickly in these genetically susceptible horses. IR develops as a result and this combines with

obesity or regional adiposity (cresty neck) to create a proinflammatory state. Chronic IR is associated with increased inflammatory adipokine release from adipose tissues and enhanced oxidative damage. This type of damage has been associated with dopaminergic neuron degeneration in horses with ECD, so EMS may accelerate the onset of disease. Until more sensitive tests become available, horses exhibiting a cresty neck should be evaluated for ECD, and those with negative results should be diagnosed with EMS. Practitioners should use their own clinical judgment when assessing patients to discern whether the horse is beginning to make the transition to ECD. In my opinion, pergolide therapy is warranted in the horse with EMS that appears to be developing ECD, even in the absence of supportive diagnostic test results.

SUMMARY

Older horses are at risk for developing ECD and pergolide is an effective treatment for the condition. Clinical signs and available diagnostic tests will confirm the presence of advanced disease, but may not be sensitive enough to detect early ECD. Horses with EMS present a diagnostic challenge because they may develop ECD at an earlier age. The owner or veterinarian must recognize the transition from EMS to ECD and initiate pergolide therapy when it occurs.

Equine Metabolic Syndrome

INTRODUCTION

Equine metabolic syndrome (EMS) is an endocrine and metabolic disorder, where insulin resistance (IR) is the primary problem encountered and this condition increases the risk of pasture-associated laminitis.

Equine metabolic syndrome is defined by the detection of chronic IR in a horse or pony. Other potential causes of IR include pituitary pars intermedia dysfunction (ECD, also called equine Cushing's disease), stress, and pregnancy, and these conditions must therefore be ruled out before the diagnosis of EMS is made. Genetic differences in energy metabolism are likely to play an important role in this disease because clients consistently report that horses are "easy keepers"with respect to their caloric needs. This syndrome is currently defined by (1) insulin resistance, (2) the presence of obesity and/or regional adiposity, and (3) prior or current laminitis. Evidence of prior laminitis comes from the history provided by the client or detection of obvious growth rings on the hooves (founder lines), which are assumed to result from previous subclinical laminitis episodes.

"Metabolic syndrome"has been used to describe this syndrome in the past, but it is preferable to use the descriptor "equine" when referring to horses and ponies (Johnson, 2002). Metabolic syndrome is a term used in human medicine to describe a set of factors that identify people who are at risk for developing coronary heart disease, stroke, or diabetes. In contrast, EMS describes a clinical syndrome that is

unique to the equine species because of its connection with laminitis. In the past, some horses or ponies with EMS have also been inappropriately labeled as "hypothyroid" after low serum thyroid hormone concentrations were detected. However, it is now known that low resting thyroid hormone concentrations can occur without thyroid gland dysfunction in horses, and clinical hypothyroidism can be diagnosed only after more advanced testing (Breuhaus et al., 2006). Equine metabolic syndrome occurs in horses and ponies. No published information is available regarding the prevalence of EMS in different breeds of horses, but based upon our experience, the disorder is most common in pony breeds, Morgans, Paso Finos, and Norwegian Fjords. We have also diagnosed EMS in Arabians, Quarter Horses, American Saddlebreds, Tennessee Walking Horses, Thoroughbreds, and warmbloods, which suggests that many breed groups are represented (Frank et al., 2006b).

Affected animals are often middle-aged (10 to 20 years of age) when EMS is first recognized, but the condition can also affect younger (5 to 10 years of age) horses. EMS is often first recognized when laminitis develops. The horse is usually being kept on pasture, and the episode occurs after the pasture has gone through a period of rapid growth (spring) or entered winter dormancy (fall). Upon closer examination, founder lines are seen on the hooves, which indicate prior subclinical laminitis episodes. Horses with EMS are predisposed to hyperlipemia, and mares may have abnormal reproductive cycles (Vick et al., 2006).

Veterinarians or farriers will sometimes recognize the physical characteristics of horses and ponies with EMS. Affected animals either suffer from generalized obesity and have an overall overweight appearance, or look more normal in appearance but have enlarged fat deposits in the neck and tailhead regions. The presence of enlarged fat deposits in these locations is referred to as regional adiposity and the thickened neck region is often called a "cresty neck."

The final part of the clinical picture comes from the history and cannot be easily measured. Horses and ponies with EMS are described as "easy keepers" because they seem to require fewer calories to maintain their body weight. This is likely to be a reflection of genetic susceptibility. Insulin is a hormone secreted by the pancreas that stimulates the uptake of glucose by tissues when sugar is abundant (i.e., after feeding). Skeletal muscle and adipose tissues are the major sites of insulin-mediated glucose uptake, but the liver also responds to insulin by increasing uptake of glucose from the blood. Insulin binds to receptors on the surface of plasma membranes and triggers a series of internal events that result in the movement of glucose transporter proteins (GLUT4) to the cell surface, facilitating rapid glucose uptake. Insulin plays an important role in the storage of energy by moving glucose into cells where it can be stored as glycogen or converted into fat.

INSULIN RESISTANCE

This condition is defined as the failure of tissues to respond appropriately to insulin. There are numerous mechanisms responsible for IR including a reduction in the density

of insulin receptors on the cell surface, malfunction of insulin receptors, defective internal signaling pathways, and interference with the translocation or function of GLUT4 proteins.

We do not know the exact path physiology of EMS, but it begins with a combination of genetic and dietary factors. Evidence for a genetic component of EMS comes from a published study examining the heritability of IR in ponies (Treiber et al., 2006) and from our own observations that the dam or sire of the patient with EMS also suffers from the disorder. The easy keeper concept is relevant to this issue of genetic susceptibility. Certain breeds or genetic lines may have undergone evolutionary adaptations to survive in harsher environments, and these horses or ponies can more efficiently convert poorer quality forages into energy. Under modern circumstances, these adaptations are unnecessary and are likely to predispose the animal to obesity. Equine metabolic syndrome may therefore begin with the genetically susceptible horse or pony grazing on lush pasture or being fed large amounts of concentrates.

As excess energy is stored as fat, adipose tissues expand through an increase in the number and size of adipocytes. Cellular functions are negatively impacted and adipose tissues release factors called adipokines that act locally and enter the circulation. Some of these adipokines exert proinflammatory effects that may contribute to the development of laminitis. Skeletal muscle tissues also accumulate lipid, which means that both of the major sites of insulin-stimulated glucose uptake become affected, and IR develops as a result. All of the pieces of the puzzle must be assembled before we can fully understand the association between IR and pasture-associated laminitis in horses and ponies. However, there are three broad mechanisms by which IR could predispose horses to laminitis: (1) insulin resistance might impair glucose delivery to hoof keratinocytes, (2) insulin resistance could alter blood flow to the foot, or (3) obesity and IR could lead to a proinflammatory state. The first theory is supported by results of a study performed by Pass et al. (1998) in which it was demonstrated that hoof tissue explants separated at the dermal-epidermal junction when deprived of glucose. Furthermore, Mobasheri et al. (2004) determined that GLUT4 proteins are found in equine keratinocytes, which suggests that insulin-stimulated glucose uptake occurs in the hoof. Studies examining the relationship between IR and blood flow have not been performed to date in horses, but insulin is known to act as a slow vasodilator in humans, and IR has been associated with a decrease in peripheral vasodilation (Yki-Jarvinen and Westerbacka, 2000). If IR is a determinant of susceptibility to pasture-associated laminitis, then what triggers the laminitis episode itself? It appears that nonstructural carbohydrates (WSC) within pasture grasses play an important role in this process. Nonstructural carbohydrates include simple sugars, starch, and fructans (polymers of fructose), and levels of these components vary considerably within grass according to geographical location, soil type, weather conditions, and time of day (Hoffman et al., 2001). These carbohydrates are likely to affect the susceptible horse in two ways. First, excessive sugar consumption could exacerbate IR as it does in diabetic humans, and second, consumption of large quantities of WSC might alter the

bacterial flora found within the large intestine. These alterations in bacterial flora are thought to increase the production of triggering factors for laminitis that may include exotoxins, endotoxins, or vasoactive amines (Bailey et al., 2002). Alterations in large intestinal bacterial flora have been induced by orally administering oligofructose (a fructan) to horses (Al Jassim et al., 2005).

MEASUREMENT OF RESTING SERUM INSULIN CONCENTRATION

This is the easiest measurement to perform and is a useful screening test because compensatory hyperinsulinemia is a common feature of IR in horses. However, there are several limitations to this test. First, serum insulin concentrations are markedly elevated when the horse is suffering from laminitis because pain and stress induce cortisol and epinephrine release, and these hormones induce IR. Testing should therefore be delayed until after the pain caused by laminitis has resolved. Second, hyperinsulinemia may not be present in the horse with mild IR, so a dynamic test (see below) is required in these cases. Finally, some older horses with chronic IR can develop pancreatic insufficiency, which will result in lower insulin levels accompanied by hyperglycemia.

Resting insulin concentrations are reliable only if samples are collected appropriately. Blood samples must be collected from horses that have been held off pasture for at least 12 hours and fed hay overnight. Grazing on pasture can raise serum insulin concentrations if the sugar concentrations are high in the grass, and grain will cause insulin levels to peak several hours after the meal is consumed. Detection of IR on the basis of resting insulin concentrations is also hindered by the wide reference ranges provided by laboratories. The upper limit of the insulin reference range at the University of Tennessee is 30 µU/mL (mU/L), but the range extends up to 300 pmol/L (43 mU/L; multiply by 7 to convert units) for the Diagnostic Center for Population and Animal Health at Michigan State University. When samples are sent to the University of Tennessee laboratory, we consider an insulin concentration above 20 µU/mL (mU/L) to be suggestive of IR and define hyperinsulinemia as >30µU/mL. High-normal glucose concentrations (>100 mg/dL or 5.5 mmol/L; multiply by 18 to convert units) are also detected in some horses with IR.

COMBINED GLUCOSE-INSULIN TEST (CGIT)

This dynamic test can be used to detect IR in the horse with a resting serum insulin concentration <30 µU/mL. The procedure involves collection of a baseline blood sample, then infusion of 150 mg/kg body weight (bwt) 50% dextrose solution, immediately followed by 0.10 units/kg bwt regular insulin. Blood samples are collected at 1, 5, 15, 25, 35, 45, and 60, 75, 90, 105, 120, 135, and 150 minutes postinfusion. IR is diagnosed by assessing both the glucose and insulin responses during the test. For the glucose response, IR is defined as maintenance of blood glucose concentrations

(measured with a hand-held glucometer) above the baseline (pre-injection) value for 45 minutes or longer. The insulin response is examined by measuring serum insulin concentrations at 0 (pre-injection) and 45 minutes. Insulinresistant horses exhibit resting hyperinsulinemia (>30 μU/mL) or show an exaggerated response to exogenous glucose. These affected horses secrete more insulin from the pancreas to compensate for IR, and the serum insulin concentration exceeds 100 μU/mL when it is measured at 45 minutes. The test can be abbreviated to 60 minutes when used in the field, but it is advisable to complete the measurements so that the time taken for the blood concentration to return to baseline can be recorded for future reference. This allows assessment of the response to diet, exercise, or medication. There is a small risk of hypoglycemia when performing this test, so two 60-mL syringes containing 50% dextrose should be kept on hand and administered if sweating, muscle fasciculations, or profound weakness are observed, or if the blood glucose concentration drops below 40 mg/dL. Note that stress is an important cause of transient IR that can significantly impact CGIT results. In one of our studies, we detected IR in healthy nonobese horses when CGITs were performed immediately after endoscopic examinations (Eiler et al., 2005). Horses must therefore remain calm prior to and during the procedure to avoid false positive results. An intravenous catheter should be used to reduce the stress associated with blood collections and this catheter should ideally be placed the night before. Since pain affects results, horses suffering from acute laminitis must be given time to recover before testing is performed. Feed deprivation also causes stress, so horses should be permitted to eat grass hay during the testing procedure.

We screen horses for IR by measuring resting serum insulin concentrations. If the serum insulin concentration is very high, it is sufficient to make the diagnosis of IR. However, horses with clinical signs of EMS that have serum insulin concentrations that fall within the reference range (<30 μU/mL) are assessed by performing a CGIT.

The goals of EMS management are to (1) reduce body fat mass to improve insulin sensitivity and control the adverse effects associated with obesity and regional adiposity (e.g., lower adipokine production), and (2) lower the risk of laminitis by improving insulin sensitivity and reducing the likelihood of sudden changes in bacterial flora within the large intestine.

MANAGING OBESITY

Individual horses should be fed according to their metabolic needs. Obese horses that are easy keepers can be placed on a simple diet of hay and a vitamin/mineral supplement. Concentrates are not necessary for these obese horses and weight loss should be promoted by restricting the horse's caloric intake until its ideal weight and body condition are achieved. This ideal point differs between individual horses and breeds because the physical stature of the animal varies considerably. The horse must be taken out of an obese state, but it is not necessary for every horse to assume an underweight condition. Weight loss strategies include dietary management and

exercise. Horses that are lame because of laminitis should not be exercised until hoof structures have stabilized, but all other affected horses should be exercised as often as possible. The horse can be walked on a lead rope, exercised on a longe line, or ridden. It is ideal for the horse to be exercised every day and it is likely that this intervention improves insulin sensitivity.

MANAGEMENT

In addition to exercise, care must be taken to avoid feeds that exacerbate IR. The horse with EMS is similar to a person with diabetes, so sugar should be avoided. Unfortunately, it is sometimes difficult to control sugar intake in horses that are grazing on pasture. Pasture grass may be the largest sources of sugar in the horse's diet. The sugar content of pasture grass varies between regions and depends upon the soil type, climate, hours of sunlight, and type of grass growing. It also varies according to season and time of day. This creates large fluctuations in sugar intake, which can exacerbate IR and potentially alter the bacterial flora of the large intestine.

Access to pasture must therefore be restricted or eliminated when managing horses and ponies with EMS. Sometimes this is only necessary for a few months until weight loss has been achieved; however, severely affected horses must be permanently housed in dirt paddocks because they are extremely sensitive to changes in pasture grass nutrient content. Once resting serum insulin concentrations have returned to normal, a horse with a history of only one episode of laminitis can be returned to pasture on a trial basis. This should be limited access that is accomplished by restricting grazing time to one to two hours per day, housing in a small grass paddock, strip grazing using an electric fence, or application of a grazing muzzle. However, these animals must be closely observed and it may become necessary to eliminate pasture access altogether if laminitis returns.

Basic guidelines for lowering the risk of pasture-associated laminitis include avoiding times when the grass is (1) turning green and growing quickly (spring), (2) first drying out at the beginning of a summer drought, (3) rapidly growing after a heavy summer rain, and (4) entering winter dormancy (fall). In general, the horse or pony with EMS should be kept off pasture when the grass is in a dynamic phase. It is also useful to recommend that clients pay attention to when their lawn needs to be mown more frequently because these are the times of the growing season when their horses should be held off pasture. Some horses with EMS have a leaner overall body condition, but have enlarged fat deposits (regional adiposity). These horses may be transitioning to pituitary pars intermedia dysfunction (ECD) or may have a leaner body condition because of adequate dietary control and exercise. If the horse is exercising strenuously or still competing, it will have a higher energy requirement and require more feed. A concentrate can be fed, but care should be taken to provide calories without exacerbating IR.

REDUCING THE RISK OF LAMINITIS

Laminitis can develop when triggering factors are released from bacteria within the large intestine after sudden changes in diet. In the case of a grain founder, this occurs when the horse breaks into the feed room and eats too much grain. There is a rapid increase in the amount of sugar arriving in the large intestine, the bacterial flora of the colon becomes altered, intestinal permeability increases, and triggering factors are released into the blood. Pasture-associated laminitis develops in a similar way, except that the sugar comes from grass consumed on pasture. Laminitis is triggered by changes in bacterial flora, but the individual horse's threshold for laminitis appears to determine whether disease develops. We hypothesize that insulin sensitivity plays an important role in determining the laminitis threshold. The horse with EMS has a low threshold for pasture-associated laminitis, and founder lines indicate that numerous subclinical laminitis events have occurred beforehand. According to this theory, improving insulin sensitivity should raise the laminitis threshold. Horses or ponies with EMS that have suffered from repeated episodes of laminitis must therefore be held off pasture to prevent both the exacerbation of IR and the triggering of laminitis. In selected cases when IR is associated with obesity, and laminitis threatens to cause permanent damage to the feet, weight loss can be accelerated by administering levothyroxine sodium (Thyro L®, Lloyd, Inc., Shenandoah, Iowa) at a 48 mg/day dosage (4 teaspoons in the feed once daily) for 3 to 6 months. Our research has shown that this drug lowers body weight and increases insulin sensitivity in obese horses. This treatment should only be prescribed by a veterinarian.

SUMMARY

Obesity and insulin resistance are important predisposing factors for laminitis in horses and ponies. Diet changes and exercise are key components of any management plan for affected horses, and restricted access to pasture is the key to success when trying to induce weight loss. Levothyroxine is a drug that can be used to accelerate weight loss and improve insulin sensitivity in obese horses when the patient is threatened by laminitis.

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