Laminitis in the Obese Mature Horse
Peripheral Cushingoid Syndrome ("Equine Metabolic Syndrome")

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Obesity is a very common medical problem with which modern horses are faced in large part because of the impositions and requirements of modern management practices. In many respects, the tendency for adult horses to develop obesity and the endocrinopathic consequences of obesity-associated insulin insensitivity closely parallels adult-onset diabetes mellitus in human beings. Non-insulin dependent diabetes (type-2 diabetes mellitus) is currently receiving remarkable international recognition as an emerging disease of widespread importance. The major extent to which type-2 diabetes is currently being acknowledged in the human populace has been directly attributed to modern life-style practices including insufficient exercise and dietary excess. Modern horse management practices call for both the imposition of protracted periods of inactivity (stall confinement) and the provision of rations that tend to contain too much starch.

The modern horse represents an excellent example of successful evolution. However, evolution equipped the equine metabolism for survival based on the seasonally-variable availability of forage (grass); the temporary development of additional body fat (relative obesity) at times when forage is plentiful provides a survival adaptation for times when conditions are harsh and forage is scarce. During periods in which forage is relatively unavailable, the body fat stores, which were never intended to become excessive, are depleted in order to provide calorific energy for survival. Under many modern horse management systems, the combination of feeding starch-rich rations over many years and protracted periods of stall confinement tend to lead to the acquisition and maintenance of substantial body fat in the domesticated horse.

The development of obesity in adult horses is attended by a risk for laminitis. In this regard, obesity in mature horses is strikingly similar to the risk for type-2 diabetes mellitus and cardiovascular diseases in obese human patients. As was once the case for obese people, obese horses are commonly diagnosed with "hypothyroidism" and treated using thyroid hormone supplementation. However, obesity and laminitis are not characteristics of *bona fide* hypothyroidism in horses. Although there is also an association between the development of laminitis and *pars intermedia* dysfunction in old horses, the tendency of younger adult horses (8 – 18 years of age) to develop laminitis in the face of obesity should not be attributed to dysfunction in either the thyroid or pituitary glands.

The term "peripheral Cushingoid syndrome" has been widely adopted by veterinary practitioners in recent years to identify these mature, adult horses that develop laminitis in the face of obesity. Use of the word "Cushingoid" implies that the clinical features of this syndrome should be attributed to excess glucocorticoids (GC) actions. As will be discussed, abnormal regulation of GC at the cellular level in some tissues may play an important role in some aspects of this condition, but the endocrinopathic characteristics of this condition are certainly not restricted to those associated with GC excess. Although the analogous human condition has been variously referred to by more than 10 different syndrome labels during the past several years, recently it was decided that the human condition would be referred to as the Metabolic Syndrome. Accordingly, we have advocated that the equine "peripheral Cushingoid syndrome" should probably be more appropriately termed the Equine Metabolic Syndrome.

Obesity and the insulin refractory state

The development of obesity in both human and equine individuals directly causes insulin insensitivity, also known as the insulin refractory state. Recent discoveries have forced us to re-evaluate our thinking about adipocytes. Fat tissue is not, as had previously been contended, simply a benign and metabolically inactive energy storage tissue. Multiple metabolically-active factors are produced by adipocytes that exert hormonal actions both locally (through paracrine and autocrine mechanisms) and via the circulation (endocrine action). These factors inhibit the action of insulin at central (hepatic) and peripheral (skeletal muscle and adipocytes) tissues. Inhibited insulin responsiveness leads to the development of "glucose intolerance". Glucose intolerance is defined as an abnormally delayed reduction in the rate by which exogenous glucose (such as that derived from food in the intestinal tract) is removed from the circulation. Consequences of glucose intolerance include persistent post-prandial hyperglycemia, prolonged release of insulin by pancreatic β-cells and fasting hyperglycemia. Disposition of a glucose load by insulin should normally entail the inhibition of hepatic gluconeogenesis and stimulation of glucose uptake by the peripheral tissues (especially liver and adipose tissue). Unlike the situation in human and feline patients, in which chronic insulin insensitivity and glucose intolerance commonly lead to pancreatic β-cell failure ("endocrine pancreatic exhaustion") and a progressive reduction in insulin secretion (non-insulin dependent diabetes mellitus), affected horses appear to be able to maintain a high level of insulin secretion in the face of insulin resistance.

An insulin refractory state can be demonstrated in obese horses with laminitis (peripheral Cushingoid syndrome) in which the fasting serum insulin concentration is often extremely high (hyperinsulinemia). In many affected obese horses, the serum insulin concentration exceeds 1,000 pmol/L (reference range, <300 pmol/L). However, overt type-2 diabetes, as suggested by hyperglycemia and reduced serum insulin concentration, appears not to occur in affected horses.

Mechanistic discussion pertaining to the development of insulin insensitivity as a consequence of obesity is beyond the scope of this article. Specific endocrine signals produced by adipocytes that have been proposed to act in the body to cause insulin insensitivity in the obese state include resistin, leptin, free fatty acids, interleukin-6, and cortisol. Adipocytes possess the steroid transformation enzyme 11β-hydroxysteroid dehydrogenase-1 (11β-HSD-1) that converts circulating cortisone to active cortisol. In the human metabolic syndrome and in certain types of equine laminitis, tissue activity of 11β-HSD-1 is increased such that the local production of cortisol (from the circulating inactive metabolite, cortisone) is increased. Local tissue dysregulation of cortisol (as a result of increased 11β-HSD-1 expression) in this syndrome is the basis for the use of the term "peripheral Cushingoid syndrome". A satisfactory explanation for the association between increased 11β-HSD-1, increased cortisol and the development of laminitis in this syndrome is currently lacking. The interested reader is directed to other sources for further information regarding the pathophysiology of insulin insensitivity resulting from obesity (see supplemental reading).

It should be noted that excessive levels of endogenous and exogenous GC represent an important cause of insulin insensitivity. Insulin insensitivity is therefore evident in equine conditions associated with excess GC including *pars intermedia* dysfunction, stress (especially the stress associated with painful laminitis) and the administration of exogenous GC such as dexamethasone and triamcinalone.

Albeit controversial, a direct laminitis-inducing action for GC has been attributed to the association between the development of laminitis in horses affected with *pars intermedia* dysfunction and in some horses that are treated using dexamethasone and triamcinalone. However, it is clear that GC do not predictably and directly cause laminitis. The novel concept that cardiovascular dysfunction resulting from insulin insensitivity and glucose intolerance is important for the pathogenesis of laminitis in these horses has received much interest recently.

Insulin insensitivity leads to endothelial cell dysfunction

In the insulin refractory state, hyperglycemia arises because the action of insulin is inhibited in hepatocytes, adipocytes, and skeletal muscle cells. Other tissues, that are not dependent on insulin for glucose uptake, are subjected to relatively high levels of glucose during periods of insulin insensitivity. Of these tissues, endothelial cells are particularly susceptible to the effect of relative glucose excess, known as glucotoxicity. Substantial evidence exists to implicate a central and critical role for endothelial dysfunction in the pathogenesis of vascular complications attributable to insulin insensitivity in human patients. Only moderate levels of hyperglycemia are needed to cause endothelial dysfunction.

Several mechanisms by which excessive glucose leads to endothelial dysfunction have been demonstrated. Increased glucose availability leads to an overall reduction in endothelial-derived nitric oxide (NO) activity and increased expression of endothelin-1 (ET-1). The combination of reduced NO and enhanced ET-1 production leads to a relatively increased state of vasospasticity because NO and ET-1 represent the two most potent endothelium-derived vasorelaxing and vasocontracting factors, respectively. In addition to the effect on endothelial regulation of underlying vascular tone, hyperglycemic states also tend to cause endothelial cells, which normally present a relatively anti-thrombotic surface to blood, to be transformed into a relatively pro-coagulative state. The reader is directed to other sources for more information on this subject (see supplemental reading).

Insulin insensitivity during stressful conditions

Any condition associated with “stress” should be regarded as a potential trigger for increased endogenous cortisol production and GC-induced insulin refractoriness. An excellent clinical example of this situation is laminitis itself. The development of painful laminitis for *any* reason leads to a pronounced stress response. Affected horses develop hypercortisolemia, hyperinsulinemia, hyperglycemia, glucose intolerance, and hypertension. Therefore, the veterinary practitioner must be careful to differentiate between stress-induced insulin refractoriness arising because of laminitic pain versus a state of insulin insensitivity being the underlying cause of laminitis. Therefore, establishing a diagnosis of obesity-associated insulin refractoriness might not be possible during bouts of painful laminitis because the pain itself will lead to hyperinsulinemia.

Obesity and laminitis

Experimental investigations pertaining to the development of laminitis in mature horses with obesity have not been reported. Almost all research pertaining to a better understanding of the pathogenesis of equine laminitis has addressed alimentary-type acute laminitis. In this regard, most investigators have used either the carbohydrate (starch) overload or Black Walnut models for the induction of acute laminitis. Both of these experimental approaches are intended to model the development of acute

laminitis as it arises when horses are affected by disturbances in the alimentary tract. We have contended that the laminitis arising in conjunction with obesity in mature horses is probably not attributable to intestinally-derived factors or circulatory changes associated with SIRS or endotoxemia. Instead, obesity-associated laminitis is a manifestation of insulin insensitivity and glucose intolerance in obese horses. Nevertheless, in both scenarios, the pathological changes at the level of the hoof that lead to clinical laminitis may be similar in that both alimentary- and endocrinopathic-type laminitis appear to involve perturbations in the regulation of blood flow through the lamellae and local oxidative stress.

Laminitis arising in conjunction with obesity is typically insidious and mild. Owners report that many affected horses have never exhibited any lameness. Horse owners commonly fail to recognize the development of the characteristic divergent growth lines at the hoof wall of affected horses. In many cases, the diagnosis of laminitis in obese horses is made by the veterinarian as an incidental finding during a routine physical examination. On further discussion with the owner, it may be discovered that, in spite of life-long ownership, the horse had never developed lameness associated with laminitis. Therefore, it appears that, in many instances, laminitis arising in conjunction with obesity may be subclinical and might not cause pain and recognizable lameness. Instead, the pathological processes within the hoof-lamellar interface progressively lead to lengthening of the lamellae, widening of the white-line zone, and divergent growth lines ("laminar lines" or "stress lines") in the hoof wall.

It has been suggested that obesity predisposes to laminitis because the increased weight leads to excessive tension in the deep digital flexor tendon (DDFT) and that heavier horses are more likely to develop laminitis because of relatively greater distractive forces at the hoof-lamellar interface. Although weight-associated tension in the DDFT surely plays a role in the morbidity of laminitis after the acute phase for any cause, the fact that pony breeds are at greater risk for the development of laminitis than horse breeds argues against the obesity factor being a simple matter of greater or lesser force in the DDFT. Interestingly, compared with horses, pony breeds tend to be refractory to insulin and glucose intolerant.

Clinical recognition and diagnostic corroboration of obesity associated with insulin refractoriness ("Metabolic Syndrome") in horses

Affected horses are usually obese and tend to be aged between 8 – 18 years. However, it should be noted that not all affected horses are grossly obese and use of the term "obesity" is often disliked by horse owners. Obesity is commonly recognized in all breeds but certain breeds appear to be over-represented (see above). The exterior appearance of affected horses commonly includes development of increased subcutaneous fat in the neck ("cresty neck") and the rump, but most affected horses tend to be distinctly obese in a generalized manner. A body score of 7 to 9 (out of 9) is often assigned to affected horses. Geldings tend to develop a "swollen sheath" because of enhanced subcutaneous adiposity. Ample adipose tissue is also identified in the omental location for most of these horses at necropsy. Horse owners invariably report that it is very difficult to reduce the weight of these horses by dietary restriction and they are commonly referred to as "easy-keepers". Affected brood mares sometimes exhibit abnormal estrous cycling and may be difficult to breed successfully.

Some breeds appear to be genetically predisposed to developing obesity and the health risks that attend it. Of note, we have suspected that domesticated Spanish Mustangs, Paso Finos, Peruvian Pasos, and the Morgan horse breed appear to be at particular risk for this condition. Compared with horses, several

pony breeds tend to be relatively insulin insensitive and prone to glucose intolerance. This difference might contribute to an explanation as to why ponies are at greater risk for developing laminitis.

Horses affected with the peripheral Cushingoid syndrome are sometimes presented to veterinarians for the treatment of laminitis. In other cases, the presence of an obese phenotype and the development of hoof wall changes consistent with chronic subclinical laminitis are recognized incidentally during a routine physical examination. On further discussion with the owner, there may be no history of prior lameness attributable to laminitic pain or a reasonable explanation for the development of laminitis in the medical history. The degree of pain associated with laminitis in obese horses is often, but not necessarily, mild. Physical examination of the affected feet commonly reveals evidence of chronic laminitis (convex sole, divergent growth lines, and widening of the white line zone). Radiographic findings may include evidence of pedal bone displacement (rotation) and pedal bone remodeling (pedal "osteitis").

The presence of other endocrinopathic conditions such as hypothyroidism and *pars intermedia* dysfunction should be ruled out using appropriate diagnostic tests. Hypothyroidism should be ruled out based on the results of a thyroid stimulation test and *pars intermedia* dysfunction should be ruled out based on the results of a dexamethasone suppression test. Both serum T3 and T4 levels tend to be low in horses affected with the peripheral Cushingoid syndrome.

Diagnosis of peripheral Cushingoid syndrome in obese horses is supported by demonstrating hyperinsulinemia in the presence of a normal or slightly elevated glucose concentration in the fasted individual. The resting plasma glucose concentration may be normal or elevated in affected horses. However, compared with other species (including humans), obese horses may develop very marked elevations in serum insulin concentration. Serum free fatty acid levels are often elevated in affected horses.

Glucose intolerance may be specifically identified and characterized based on the results of an intravenous glucose tolerance test (IVGTT). After the horse has been fasted for 12 hours, a resting (zero-time) blood glucose determination is made and the horse is then injected with glucose (0.5 g/kg of body weight, IV, over approximately 3 to 4 minutes) using a 50% dextrose solution. Blood glucose determinations are determined at every 30 minutes for 3 hours while the horse is fasted. A state of glucose intolerance is suggested by a failure of the blood glucose to return to the baseline within 3 hours. Other factors that might cause false-positive identification of the insulin refractory state and hyperinsulinemia include pain from laminitis, stress/excitement, exogenously-administered GC, and *pars intermedia* dysfunction.

At the present time, diagnosis of the peripheral Cushingoid syndrome (obesity-associated insulin refractory state) is therefore based on consideration of the physical appearance of the patient, results of routine blood tests, fasting hyperinsulinemia, elimination of other reasonable causes of similar findings and the results of glucose tolerance testing.

Treatment and prevention of the obesity-associated insulin refractory state in horses

The development of obesity and obesity-associated insulin refractoriness in mature horses and ponies may be genetically determined to some extent, and therefore should be suspected in certain breeds and familial lines. The common practice of feeding growing and mature horses and ponies rations characterized by a high glycemic index (excessive grain) should be discouraged. Careful attention to ration formulation should include consideration of the size of the horse and the level of physical activity. Many horses develop obesity because they are fed too much grain in respect to their level of exercise; obese horses are commonly stall-confined for protracted periods and exercised at mild-to-moderate levels of energy expenditure for only short periods during the day.

Ideally, consultation with an equine nutritionist should be recommended. A carefully-planned low-starch ration (low glycemic index) containing high quality forage that is balanced with respect to minerals and vitamins is recommended for the management of horses affected with the peripheral Cushingoid syndrome. The widespread practice of feeding inappropriately high quantities of grain to younger horses should be discouraged; it is these same horses that tend to progress to obesity in middle age and are prone to laminitis.

As is the case in human beings, the crucial and most effective preventive and treatment strategies are those associated with both increased physical activity and dietary-induced weight reduction. Increased exercise has been shown to improve insulin sensitivity in horses and ponies. For horses affected with painful laminitis, increased activity might be detrimental until laminitis has been controlled. Effective management of laminitic pain with enable the horse to exercise and will be associated with a reduction in the secretion of endogenous GC.

Although dietary thyroid hormone supplementation is commonly advocated in the management of obesity and obesity-associated laminitis, this practice has been discredited in the human field. Inappropriate thyroid supplementation may certainly lead to weight reduction in these patients by creating a state of iatrogenic hyperthyroidism. Potentially adverse side-effects of inappropriate thyroid supplementation, which have been well-documented in human patients, have received little attention in equine patients. Similarly, there is no basis for the treatment of insulin refractoriness in obese patients using either pergolide or cyproheptadine, both of which should be reserved for the management of hyperadrenalocorticism associated with *bona fide pars intermedia* dysfunction.

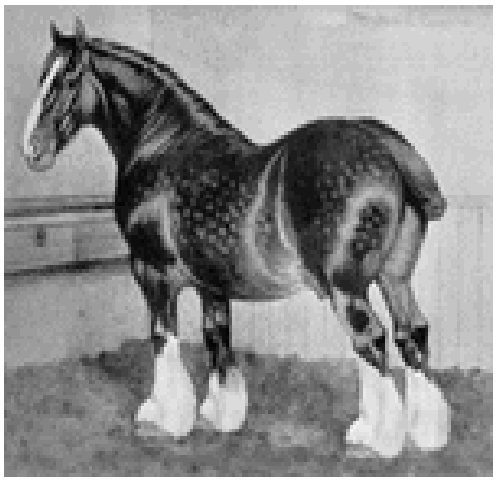
In light of the evidence that oxidative stress is important for the pathogenesis of endothelial dysfunction in the obese state and that anti-oxidant strategies have been shown to improve endothelial function in affected individuals, dietary supplementation with high levels of vitamin E (10,000 units, PO, bid) might be logically and safely used in the management of obese horses (in conjunction with weight reduction, dietary changes and increased levels of activity).

Enhanced platelet aggregability in the obese patient might be addressed using orally-administered aspirin therapy. Pharmacological reversal of the vasoconstrictive actions of endothelin-1 may be useful for the management of laminitis associated with obesity, however these agents have not yet been investigated in horses. Similarly, inhibitors of the renin-angiotensin system may reverse some of the pathological vascular changes associated with endothelial dysfunction in obese horses, but these drugs

have not been investigated in horses. Recently-introduced anti-diabetic (insulin-sensitizing) drugs that increase the action of insulin in peripheral tissues, such as the thiazolidinedione, metformin, are deserving of investigation in equine patients. Thiazolidinedione anti-diabetic agents are also potent inhibitors of 11β-HSD1 and appear to preferentially and selectively reduce visceral fat accumulations in humans. However, to our knowledge, none of the many drugs aimed at human patients have been investigated in horses at this time. The role of antiglycemic, antidiabetic agents in the management of type-2 diabetes in human patients has been thoroughly reviewed elsewhere.

There has been some speculation that inhibitors of enzymes involved in the biosynthetic pathway for cortisol (including metyrapone, aminoglutethamide, ketoconazole, miconazole and trilostane) might be useful for the management of both *pars intermedia* dysfunction and metabolic syndrome. However, at this time few data have been published to support efficacy and safety for administration of these pharmaceuticals in equine patients. Trilostane (Modrenal, Stegram Pharmaceuticals, UK) is a 3β-hydroxysteroid dehydrogenase inhibitor, that acts to inhibit adrenal steroidogenesis. In one study, trilostane (0.5 – 1.0 mg/kg, po, sid) caused improvement in both the clinical signs (laminitis, polydipsia/polyuria, lethargy) and results of endocrinological tests in horses affected with *pars intermedia* dysfunction. Furthermore, treatment with trilostane reduced the quantity of phenylbutazone that was needed for the management of pain in those horses that were affected with severe laminitis. During a concurrent investigation, trilostane also caused clinical improvement in horses affected with the peripheral Cushingoid syndrome (Cathy McGowan, personal communication). In other studies, the effectiveness and safety of trilostane has been questioned.

Although insulin insensitivity has also been attributed to specific deficiencies of chromium, inorganic phosphate, magnesium, and vanadium, the extent to which deficiencies in these micronutrients is likely to contribute to the morbidity of obesity in equine patients is likely insignificant. Chromium supplementation has been reported to improve insulin sensitivity in other species but in one equine study, orally-administered chromium L-methionine (0.02 mg/kg of body weight) failed to improve insulin sensitivity in old mares. Further investigation regarding demonstration of any therapeutic value for either chromium, magnesium, or vanadium supplementation for insulin insensitive horses is warranted.



Treatment of Equine Metabolic Syndrome

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Metabolic syndrome (MS) represents a common and growing health problem for horses that has previously been classified as hypothyroidism, peripheral Cushingís disease or pre-Cushingís syndrome. Insulin resistance (IR), hypertension, an abnormal plasma lipid profile, and obesity generally characterize the MS as described in human beings. Most instances of human MS are attributable to the combined effects of inappropriate dietary intake, insufficient physical inactivity, and the development of obesity in genetically susceptible individuals.1 Substantive discussion regarding the pathogenesis of cardiovascular disease in MS is beyond the scope of this communication and the reader is referred elsewhere1-4 for more details. It should be noted, however, that the extent to which the equine MS resembles the human condition deserves further investigation.5

Under the constraints and luxuries afforded by contemporary management practices, domesticated horses tend to be fed rations that are broadly excessive with respect to the metabolic requirements for the level of physical activity to which they are subjected and/or provide calories in a concentrated form that is far removed from the natural diet. It is common practice for horses to be fed grain-rich rations during long periods of physical inactivity. Moreover, some predominantly forage-based rations are based on improved pastures and hays that are considerably higher in soluble carbohydrates (non-fiber /nonstructural carbohydrates) than wild/native grass strains. The manner in which domesticated horses are fed far exceeds in both quantity and quality the dietary intake for which the species evolved in nature. Horses have inherited ìthrifty genesî which permit highly efficient use of their dietary intake, leading to heightened ability to endure periods of environmental harshness.6 However, when presented with an abundance of food resources, susceptible horses quickly develop an obese phenotype, especially when that excess food is coupled with restricted physical activity.

Fat tissue is not, as previously held, simply a benign repository of stored energy. Adipocytes represent an important source of numerous diverse hormones (adipokines) that play a role in regulation of body mass and body composition. Further, there is increasing recognition that not all adipocytes are identical, as some are more important from the perspective of producing adipokines. For example, in humans, omental adipocytes are endocrinologically more significant

than adipocytes at subcutaneous locations. Hence, omental (intra-abdominal) adiposity is associated with greater risk for cardiovascular disease than subcutaneous adiposity. The accretion of adiposity is attended by the production of excessive quantities of endocrine signals, including leptin, resistin, adiponectin, free fatty acids, and certain pro-inflammatory cytokines (TNF-α and IL-6). Furthermore, omental adipocytes possess the enzyme 11β-hydroxysteroid dehydrogenase-1 (11β-HSD-1) that converts circulating inactive cortisone to the physiologically active glucocorticoid, cortisol.7 Many of the adipose-derived endocrine signals, including cortisol, directly inhibit the action of insulin and cause IR. Hyperinsulinemia has been shown to stimulate proliferation of vascular smooth muscle cells.

Elevated production of adipose-derived endocrine signals is believed to represent the link between obesity, IR and the risk for development of cardiovascular disease in human patients. Although it is suspected that the similar situation exists with respect to risk of laminitis in some obese adult horses, further work is needed to better characterize any pathophysiological relationships between obesity, hyperinsulinemia, IR and laminitis in horses. The MS is probably more likely to develop in animals with inherited tendencies toward IR and in which the development of obesity represents a compounding factor. The relative IR associated with pony breeds has been recognized for >30 years.

Veterinarians should consider a diagnosis of MS in adult horses that are recognized as obese and in which laminitis has been identified, or in any case of unexplained laminitis.5 Other physical characteristics of MS in horses include abnormal body fat distribution (thickened, "cresty" neck, fatty accretions at the tail head and near the shoulders, fatty thickening in the prepuce). Affected broodmares are commonly reported to be infertile and often exhibit abnormal cycling. Easy weight gain usually occurs on caloric intakes that are well below those that would be predicted to maintain a normal body weight. Polyphagia is common. Polyuria and polydipsia may be seen in those horses that tend to be severely hyperglycemic. It should be noted that not all affected horses are obese and development of MS is believed to predispose to laminitis in some horses in which laminitis has not yet occurred. Currently, demonstration of IR represents the most useful clinical approach to a diagnosis of MS in horses. Although the use of euglycemic hyperinsulinemic clamping8 represents the best method for characterization of IR, the simple demonstration of hyperinsulinemia and mild-to-moderate hyperglycemia (110 to 140 mg/dL) in fasted horses is clinically practical and strongly suggests that IR is present. Hyperinsulinemia is a far more consistent finding than hyperglycemia, however, and a presumptive diagnosis can be made based on identification of hyperinsulinemia alone, provided that grain has not been fed for a minimum of 5 hours prior to testing. Alternatively, an intravenous glucose tolerance test (IVGTT) in IR-affected horses shows plasma glucose concentration failing to return to the reference range within 90 to 120 minutes.9 Use of appropriate diagnostic tests to rule out other, potentially similar endocrinopathic conditions such as hypothyroidism and pituitary *pars intermedia* dysfunction (pituitary Cushingís disease, PPID) lends support to the diagnosis of MS. In some affected horses, the fasting plasma triglyceride concentration is mildly-to-moderately elevated.

When animals are obese, weight reduction represents the key therapeutic objective. In the human condition, modest weight reductions in the order of 5% to 10% are associated with substantial clinical improvement in a many of the concomitant aspects of MS (decreased IR, improved glycemic control, reduced hypertension, and improved lipid values). Previous work in ponies has shown that significant improvements in IR can be achieved using a combination of controlled intake of food and enhanced physical conditioning.10 Exercise leads to increased glucose uptake and the utilization by skeletal muscle by insulin-independent mechanisms that persist for up to 24 hours. However, when present, painful laminitis in equine patients necessarily precludes enhanced physical exercise for the management of obesity and IR. Furthermore, stress associated with the development of laminitis leads to activation of neuroendocrinological mechanisms (such as increased cortisol secretion) that tend to further promote the persistence of IR.

The most important aspect of feeding a horse with IR/MS is limitation of the soluble carbohydrate content of the diet. Simply eliminating grain products and use of a hay only diet may result in dramatic improvements in laminitis pain within the space of a few days. The glycemic index (GI) is a nutritionistís tool for describing the effect of a particular food on blood glucose compared to a reference food.11 In people, an elevation in blood glucose after consuming 10 to 50 grams of a test food is compared to the level seen after consuming an equivalent amount of pure glucose and expressed as a percent. Therefore, glucose has a GI of 100. A similar scale has been devised for horses, with oats being used as the reference food. According to one study (Anne Rodiek, Department of Animal Sciences and Agricultural Education, California State University), feeding of corn, barley, or oats with 10% molasses produced a blood glucose elevation equal to or greater than plain oats (GI 100 or higher). The safest feedstuff in terms of maintaining blood glucose was plain beet pulp, with a GI of 1, followed by rice bran at 22, Bermuda hay 23, alfalfa hay 26, alfalfa cubes 30, Timothy hay 32, wheat bran 37, carrots 51 and Vetch blend hay 53.

These figures are extremely helpful but can only be used as a guide when formulating an individual horse's diet, since "grass hay" can cause wide variations in blood sugar response. This is directly linked to the soluble carbohydrate content of the hay, not necessarily to the species/hay type. Growing conditions, stage of growth when cut and drying conditions all influence soluble carbohydrate content. Fresh grasses will always contain more sugar than hay as the grass will continue to metabolize a significant amount of its stored sugar during the drying process.

Hays for IR horses should ideally contain no more than 10% sugar and starch combined. This can only be accurately predicted based on the results of hay analysis. The Dairy One laboratory in Ithaca, New York (www.dairyone.com, 800-496-3344) is the industry leader in carbohydrate analyses and can provide a breakdown by total NFC (non-fiber carbohydrates = sugars, starch, and some soluble fibers), total NSC (nonstructural carbohydrates = sugar and starch) and specific breakdown as to % of sugar and % starch. A suitable low NSC/low sugar hay should be the cornerstone of the diet. Forbidden items include grains in any form (even "high fiber", "complete" or "senior" feeds), carrots, apples, wheat bran (usually contains contaminating high starch flour), molasses added to beet pulp (although this can be rinsed off before feeding) and

fresh grass. Alfalfa may be acceptable from a sugar and starch testing standpoint and inclusion in the diet at a rate of 10 to 15% of the caloric intake helps guarantee adequate crude protein intake, improves palatability, may be a carrier for supplements (cubes or pellets) and increase calcium intake. However, for reasons that are unclear, some IR/MS horses do not tolerate alfalfa in any amount without developing laminitis or gaining excess weight.

Once an appropriate hay has been identified, the question becomes how much to feed. A common mistake is to restrict intake too greatly, which is dangerous in ponies due to potential hyperlipemia. In both horses and ponies, severe calorie restriction is not helpful as insulin and glucose responses to feeding are often higher in animals on an inadequate calorie intake. For grass hays with an average DE (digestible energy) content of between 0.65 and 0.75 Kcal/lb, feeding 1.5 to 2.0% of the estimated target ideal body weight works well in most cases. Therefore, a horse with a target body weight of 1000 pounds would be fed from 15 to 20 pounds of hay/day. Horses that are stalled for a significant portion of the day usually need the lower intakes while those moving in a group/herd situation can often actually be allowed more.

These horses do very well on a hay only diet. Beet pulp can be safely fed and is useful as a carrier for supplements, and helps owners who feel they must be feeding their horses something in addition to forage. Beet pulp is more digestible than hay, having a caloric value roughly equivalent to plain oats. When feeding less than a pound (dry weight) per day, no adjustment in hay intake is necessary. At daily amounts of a pound or higher, it may be necessary to cut back on the quantity of hay fed at a rate of 1.5 lbs less hay for each pound of beet pulp. Commercial products that contain any type of grain should be avoided. In our opinion, the two best commercial feeds are Triple Crown's Triple Crown Lite™, which is also highly mineral fortified, and McCauley Brother's Alam™.

Dietary deficiencies and imbalances develop in people with IR and antioxidant nutrients have been shown to help protect against vascular endothelial damage. 12 The same may be true in horses. In addition to information regarding crude protein, digestible energy (specifically for horses), NFC/NSC and sugar/starch levels, the hay analysis should include information regarding calcium, magnesium, phosphorus, copper, zinc, manganese and selenium. The intake of each individual mineral should be set at a minimum of 150% of current NRC minimums. Ratios and amounts are as follows: 1) Ca:P:Mg between 1.5:1:1 to 2.0:1:1; 2)Cu:Zn:Mn 1:2.5 to 3:3; 3)Cu:Fe maximum of 1:10; 4)Selenium total from all sources 1 mg/100 kg body weight; 5)Iodine total from all sources 1 mg/100 kg body weight; 6)Chromium 0.5 to 1.0 mg/100 kg body weight; 7)Vitamin E 400 IU/100 kg body weight; 8)Vitamin C 500 mg/100 kg body weight (hold for hays with iron of over 150 ppm); 9)Lysine 1500 mg/100 kg body weight; 10)Methionine 500 mg/100 kg body weight; 11)Ground stabilized or freshly ground whole flaxseed, 0.5 oz/100 kg body weight.

Studies in people as well as horses, have shown that the addition of fat to a meal decreases the glucose and insulin response. However, long term high fat diets worsen IR in some species and in ponies. Horses may be more resistant to this effect, but until it is confirmed that increased fat intake does not pose a risk for horses with IR, fat/oil supplementation should be avoided. Although it has been suggested that monounsaturated fats (e.g. olive oil) might be helpful in controlling equine hypertriglyceridemia, further studies are clearly needed.

High protein diets have yielded mixed results, or have been detrimental, in IR horses. Most amino acids are also potent triggers of insulin release and insulin is required for normal cellular uptake of amino acids. Adequate, but not excessive, protein is advisable. Grass hays containing 7.5% protein and consumed at a rate of 2% body weight/day will meet crude protein requirements. At feeding rates of 1.5% of body weight/day, 10% protein hay is needed. Because grass hays are typically low in lysine, this essential amino acid should be supplemented (see above). Methionine supplementation, advocated in support of good hoof quality, is not recommended for horses affected with IR, since methionine is metabolized to homocysteine, elevated levels of which have been shown to be detrimental for endothelial function.13

Free choice access to unlimited grass should be avoided for horses affected with the IR/MS. Plant stresses of any type, including overgrazing, cold temperatures and insufficient water, increase the concentration of sugar in a grass. Sugars are also concentrated in the portions of grass closest to ground level. Laminitis commonly develops in IR/MS-affected horses that have had access to a very short, overgrazed or mowed paddock or pasture. Because of the fact that grass sugar content can change dramatically in as short a period as a few hours, allowing IR/MS horses to graze is inherently risky. The safest approach is to avoid fresh grass entirely. Horses can be turned out with completely or partially taped over grazing muzzles. If attempting to allow some consumption, owners must be carefully instructed to monitor the horse daily for weight gain, a change in abnormal fat deposits (e.g. crests becoming more hard/firm) and early signs of laminitis such as less spontaneous movement, increased digital pulses, change in temperature of the feet and reluctance to turn in a small circle.

As noted above, horses with MS are often misdiagnosed with hypothyroidism. There is an association between obesity and low thyroid hormone levels in some other species and some horses with MS have low levels of circulating thyroid hormones.5 However, endocrinological changes associated with obesity lead to low thyroid hormone levels and low levels of thyroid hormone do not primarily cause obesity in horses following surgical thyroidectomy.14 The existence of *bona fide* primary hypothyroidism in horses is rare. Therefore the cause of low levels of thyroid hormones in these horses is more likely attributable to pituitary-dependent or secondary hypothyroidism resulting from insufficient production of TSH or blunted TRH-induced TSH release. Supplementation or treatment of these conditions with thyroid hormone may not be appropriate.

The historical use of thyroid hormones for inducing weight loss in obese humans has, for the most part, been replaced with more physiologic methods. Undoubtedly, pharmacologic doses of thyroid hormones administered to obese humans results in weight loss and the same is likely true in horses (iatrogenic hyperthyroidism). Weight loss occurring during thyroid hormone treatment is attributable to increased oxygen consumption and protein catabolism. Most of the increase in oxygen consumption results from stimulated lipolysis and the remainder by catabolism of protein. However, more than two-thirds of the thyroid-stimulated weight loss is due to the breakdown of lean body mass rather than loss of fat. Potentially more harmful than the loss of lean muscle is the effect of inappropriate thyroid hormone supplementation on cardiac function. Thyroid hormones modify the chronotropic and inotropic properties of cardiac muscle and, at high doses, will increase the mass of the heart. Since obesity itself can increase cardiac

workload, the added cardiac load imposed by thyroid hormone treatment could be deleterious. In addition, follow-up of human patients treated with thyroid hormones to induce weight loss has shown disappointing long-term results.

The justification for exogenous thyroid hormone administration to induce weight loss in obese horses is questionable at best and there have been no well-designed studies to determine if such supplementation is either effective or safe. Thyroid hormones do facilitate insulin-mediated glucose uptake by cells in other species, but this potentially beneficial effect may be overshadowed by the fact that thyroid hormone also increases intestinal glucose absorption promoting the tendency to hyperglycemia seen in horses with MS. Despite the continued controversy regarding thyroid hormone supplementation of horses affected with MS, its use remains popular among practitioners because of perceived clinical improvement of the animal's energy level and attitude. Thyroid hormone supplementation should be attended by frequent monitoring to avoid over-supplementation, maintaining T3 and T4 within normal limits. Tapering-off of supplementation is recommended as the clinical status and insulin levels improve and it is not recommended that affected horses be diagnosed with hypothyroidism *per se*.

Although both pergolide and cyproheptadine are useful for the management of signs caused by PPID, these drugs are not indicated for the treatment of obesity or IR (MS), since they suppress pancreatic insulin secretion. There are anecdotal reports that both drugs have resulted in clinical improvement in horses affected with laminitis and IR. However, since diet control is used simultaneously with introduction of these drugs, it is generally impossible to determine specifically drug-related responses. Nevertheless, this observation raises the intriguing question as to whether MS is a risk factor for Equine Cushing's Disease.

Trilostane is a 3β-hydroxysteroid dehydrogenase inhibitor that has been useful for the management of hyperadrenalocorticism in other species. Specifically, this drug inhibits cortisol secretion at the level of the adrenal cortices. Although it has been shown that trilostane may be helpful for the management of PPID in some horses15, it is not logically indicated in the treatment of metabolic syndrome because adrenal cortical cortisol secretion is not increased. Trilostane is not currently available for treatment of horses in the USA.

It has been proposed that selective inhibitors of 11β-HSD-1 should be useful for the management of MS in humans.7 We have demonstrated increased 11β-HSD-1 activity in some horses affected with laminitis.16 Licorice, an extract of the roots of *Glycyrrhizia glabra*, contains acids which non-selectively inhibit both isoforms of 11β-HSD. A synthetic water-soluble analogue of these licorice derivatives, carbenoxolone, had been used in people, but was discontinued due to unacceptable side-effects. Currently, a selective inhibitor of 11β-HSD-1 is not available for the treatment of human or equine patients.

Numerous drugs have been made available for the management of obesity and MS in people. Broadly speaking, there are four distinct pharmacological strategies: reduction of caloric excess (e.g. appetite suppressants, fat absorption inhibitors, stimulators of energy expenditure); improvement of lipid profile (e.g. bile acid sequestrants, cholesterol absorption inhibitors); improvement of glucose homeostasis (anti-diabetic drugs such as the thiazolidinediones, biguanides and sulfonylureas); and lowering of blood pressure (e.g. ACE inhibitors, calcium

channel blockers, and beta blockers). It is unlikely that any of these drugs have clinical practicality for the treatment of horses.

There role of hypertension in equine MS has not been investigated. Dyslipidemia as a feature of MS has also been inconsistently characterized in equine patients. Strict control of dietary intake represents the most effective part of treatment for obesity and MS in this species. The development of marked hyperinsulinemia that persists for many months, possibly years, signifies that the horse's body is being subjected to inappropriately high levels of glucose (ration with a high glycemic index, such as those containing molasses and grain) Unlike other species (human and feline) in which protracted IR (hyperinsulinemia) is eventually complicated by failure to maintain insulin production (β-cell exhaustion and type-2 diabetes mellitus), horses appear to be able to sustain high insulin output in the face of IR. Therefore, it is reasonable to conclude that pharmacological interdictions that might promote the action of insulin (insulin sensitizes) could be beneficial for the management of IR in horses. To that end, we have treated a small number of IR-affected horses using the biguanide, metformin. Although metformin appears to be effective for the management of IR in some horses, further investigation pertaining to potential side effects and pharmacokinetic data are needed.

The ability of veterinarians to recognize, diagnose, and treat MS is currently hampered by inadequate basic information about this condition in horses. Further work is needed regarding the role of IR for the pathogenesis of laminitis and in better classifying the metabolic characteristics of this condition in horses.

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