

CONSENSUS STATEMENT

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ECEIM consensus statement on equine metabolic syndrome

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Equine metabolic syndrome (EMS) is a widely recognized collection of risk factors for endocrinopathic laminitis. The most important of these risk factors is insulin dysregulation (ID). Clinicians and horse owners must recognize the presence of these risk factors so that they can be targeted and controlled to reduce the risk of laminitis attacks. Diagnosis of EMS is based partly on the horse's history and clinical examination findings, and partly on laboratory testing. Several choices of test exist which examine different facets of ID and other related metabolic disturbances. EMS is controlled mainly by dietary strategies and exercise programs that aim to improve insulin regulation and decrease obesity where present. In some cases, pharmacologic aids might be useful. Management of an EMS case is a long-term strategy requiring diligence and discipline by the horse's carer and support and guidance from their veterinarians.

KEYWORDS

EMS, endocrinopathic, insulin, laminitis

Abbreviations: BCS, body condition score; BM, body mass; BPM, beats per minute; CGIT, combined glucose insulin test; DMI, dry matter intake; EDC, endocrine disrupting chemicals; ELISA, enzyme linked immunosorbent assay; EMS, equine metabolic syndrome; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; HMW, high molecular weight; HR, heart rate; ID, insulin dysregulation; IGF-1, insulin-like growth factor 1; IR, insulin resistance; IRT, insulin response test; MAP kinase, mitogen-activated protein kinase; NSC, non-structural carbohydrates; OGT, oral glucose test; OST, oral sugar test; PPID, pituitary *pars intermedia* dysfunction; RIA, radioimmunoassay; SEL, secondary epidermal lamellae; SGLT2, sodium-glucose co-transporter 2; TRH, thyrotropin-releasing hormone.

1 | INTRODUCTION

Experimental studies in the 1980's recognized an association between insulin dysregulation (ID) and laminitis in ponies.^{1,2} Equine metabolic syndrome (EMS) was more thoroughly described subsequently³ and, in 2010, an American College of Veterinary Internal Medicine consensus statement on EMS was published.⁴ The advantage of recognizing EMS is to identify animals with increased risk of laminitis and to allow implementation of evidence-based prevention strategies. The aim of

this ECEIM consensus statement is to summarize and appraise more recent scientific evidence in order to optimize recommendations on how to recognize and manage the syndrome in practice.

2 | DEFINITIONS

Equine Metabolic Syndrome is not a disease per se but rather a collection of risk factors for endocrinopathic laminitis. The key central and consistent feature of EMS is ID.⁵ The term ID is used to indicate disturbance of the balanced interrelationship among plasma concentrations of insulin, glucose, and lipids. Insulin dysregulation can manifest in several ways including 1 or more of basal hyperinsulinemia; an excessive or prolonged hyperinsulinemic response to oral or IV carbohydrate challenge, with or without an excessive or prolonged hyperglycemia ("glucose intolerance"), and tissue insulin resistance (IR). Hypertriglyceridemia can also be a consequence of IR (Figure 1).

Obesity is defined as increased adiposity that has a negative impact on the health of the affected individual. This may be manifest as 1 or more of generalized or regionally excessive fat accumulation^{6,7} a predisposition to weight gain and resistance to weight loss.⁸ EMS is usually associated with obesity, although exceptions occur.⁹ Further inconsistent features of EMS comprise cardiovascular changes including increased blood pressure, heart rate (HR) and cardiac dimensions^{9,10}, and adipose dysregulation manifesting as abnormal plasma adipokine concentrations including hypoadiponectinemia and hyperleptinemia.^{7,11}

Laminitis is the primary clinical consequence of EMS. However, horses with EMS might also be at risk of additional problems including hyperlipemia and critical care-associated metabolic derangements including hyperglycemia and hypertriglyceridemia. Additional clinical concerns including preputial and mammary edema, mesenteric lipoma, inappropriate lactation, and subfertility in mares and stallions were also considered by the panel although it was concluded, pending further evidence, that these might simply be obesity-related rather than associated with EMS.

3 | DIFFERENTIAL DIAGNOSIS

Laminitis associated with ID can also arise in association with glucocorticoid administration and pituitary *pars intermedia* dysfunction (PPID).

Additionally, nonendocrinopathic causes of laminitis can arise in association with systemic inflammatory response syndrome and excessive weight bearing. However, it should be remembered that EMS can serve as a contributory factor in laminitis resulting from other causes.

Adiposity is not inextricably linked with ID, and it is possible for equids to have EMS in association with a lean phenotype or to have excessive fat depots without the concurrent presence of ID or EMS. Thus, it is vital to demonstrate the presence of ID in an overweight animal before a diagnosis of EMS is made.

4 | EPIDEMIOLOGY

There is little epidemiological data relating to the prevalence of EMS although the prevalence of its components has been evaluated by some studies. The prevalence of hyperinsulinemia in populations of horses has been reported in a few publications with 27% of ponies being hyperinsulinemic in an Australian study,¹² 22% of horses in a US study,¹³ and 18% of healthy, nonlaminitic horses in another US study.¹⁴ Published cases of EMS largely involve British native breeds,^{6,7,9} and cases of primary endocrinopathic laminitis were more likely to occur in British native ponies compared to Nordic ponies, cold-blooded horses, and warm- and hot-blooded horses.¹⁵ Breed differences in insulin sensitivity can also occur, as was demonstrated with ponies and Andalusian horses showing reduced insulin sensitivity compared to Standardbred horses.¹⁶

Equine metabolic syndrome appears to be more common in physiologically inactive animals, perhaps because of a beneficial effect of exercise on insulin regulation as well as decreased adiposity via increased energy expenditure.^{17–19} Additionally, certain predisposed breeds such as Shetland ponies, donkeys, and miniature horses are frequently not exercised as much as many other breeds as part of standard management. Studies have generally found insulin concentrations to be significantly higher in older versus younger horses and ponies.^{12,20–22} Circulating adiponectin concentrations are also lower in older animals compared to younger animals, consistent with an age association with ID.²³ Sex does not appear to influence most markers of ID in normal or laminitic ponies and horses.^{20,24–26}

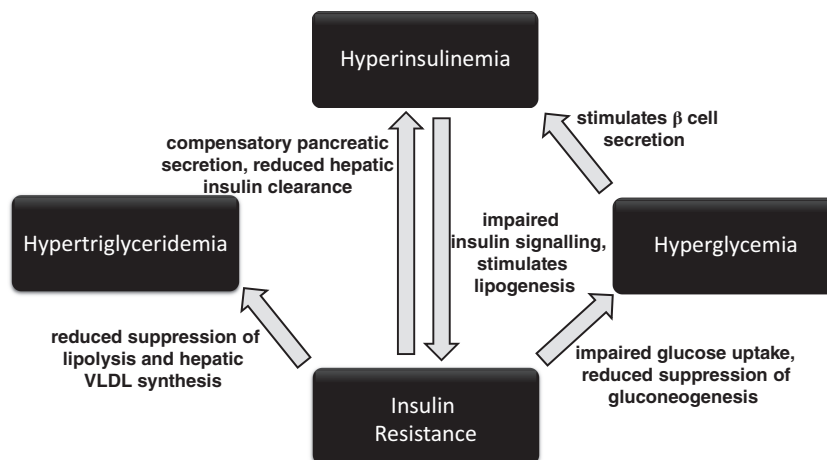


FIGURE 1 The interrelated components of insulin dysregulation

The prevalence of obesity in various equine populations ranges from 21% to 45% in the United Kingdom.^{27–31} In other countries, obesity occurs in 10% of mature Icelandic horses in Denmark,³² 8%–29% of horses in Canada,^{33,34} 24.5% of Australian pleasure horses and ponies,³⁵ and 51% of mature light-breed horses in the United States.³⁶ Regional adiposity, based on a cresty neck score >3/5, was present in 33% of horses in southwest England.³⁷ Draught-type, cob-type, British native and Welsh breeds,²⁹ Shetland ponies,³⁵ Rocky Mountain Horses, Tennessee Walking Horses, Quarter Horses, Warmbloods, and mixed-breed horses were all more likely to be obese compared to Thoroughbreds.³⁶ Animals described as “good doers,” animals used for pleasure riding, non-ridden animals, and more dominant individuals were more likely to be obese.^{29,38} Finally, in Sweden, professional equine establishments and premises in more rural regions had fewer problems with overweight animals, whereas premises that kept other species for meat production were more likely to have overweight horses.³⁹

The effects of season on components of EMS remain quite unclear with several studies having contrasting findings for regional and generalized adiposity,^{28,33,37,39} insulin,^{9,20,40–43} adiponectin,^{24,44} leptin,⁴⁵ and triglycerides.^{9,46} Pregnancy-associated ID occurs in pregnant mares,^{42,47,48} although hyperinsulinemia does not always occur.^{42,49}

Endocrine disrupting chemicals (EDCs) are associated with metabolic syndrome in humans.⁵⁰ Preliminary data demonstrated that horses from farms within 30 miles of EDC disposal sites were more likely to have had laminitis, and had laboratory evidence of ID, suggesting EDC exposure might be an EMS risk factor.⁵¹

5 | PATHOPHYSIOLOGY

5.1 | Insulin dysregulation

Insulin dysregulation plays a central role in EMS and hyperinsulinemia is probably the most important pathophysiologic feature of ID in horses.⁵² Although hyperinsulinemia might often be simply a compensatory response to systemic IR, resting and postprandial hyperinsulinemia can occur to a greater extent than explained by IR or even occur independently of IR.^{52,53}

Oral administration of glucose stimulates a greater insulin secretion than IV administration of glucose in ponies^{52,54} indicating that the gastrointestinal tract releases factors that augment glucose-induced pancreatic insulin secretion. At least 3 hormonal factors, or incretins, are known to exist in the horse, namely gastric inhibitory polypeptide (GIP) and glucagon-like peptides 1 and 2 (GLP-1, GLP-2). The relative contribution of these incretins to insulin production varies considerably among species and, in horses, an estimated influence of glucose, GLP-1 and GIP on insulin response to oral glucose administration was 76%, 23%, and 2% respectively.⁵² Active GLP-1 clearly stimulates insulin secretion in horses,^{52,55} although its role in ID remains unclear.^{55–57} Glucagon-Like Peptide 2 is a further incretin with no direct effect on insulin secretion, although it increases glucose bioavailability via gastrointestinal effects. Its role in EMS is also unclear.⁵⁸

It has generally been found that chronic feeding of a diet high in nonstructural carbohydrates (NSCs) will decrease insulin sensitivity and adiponectin concentrations compared to forage or fat-rich diets.^{17,59–62}

However, the association of dietary NSC intake and IR is not straightforward, and more recent work suggests adaptation to high NSC diets can actually improve glucose tolerance and tissue insulin sensitivity, but induce an exaggerated postprandial insulinemic response.^{53,63}

Decreased hepatic clearance of insulin might also contribute to hyperinsulinemia. More than 70% of the insulin secreted by pancreatic beta cells is normally cleared from the portal blood by the liver in horses, with evidence of decreased hepatic insulin clearance in horses with obesity and IR.⁶⁴

5.2 | Development of laminitis

Hyperinsulinemia induces laminitis in horses.^{65–67} Field-based observations have shown an association between hyperinsulinemia, or other components of ID, and laminitis,^{6,7,11,68,69} and clinical laminitis can be induced by 48–72 hours of insulin infusion in euglycemic ponies⁶⁵ and horses⁶⁶ (both studies mean insulin 1036 μ U/mL). Laminitis lesions, but not lameness, were experimentally induced by 48 hours of glucose infusion inducing hyperglycemia (mean 11 mmol/L) and endogenous hyperinsulinemia (mean 208 μ U/mL⁶⁷), giving an indication of the threshold degree and duration of hyperinsulinemia required to trigger laminitis.

The resultant lesions in endocrinopathic laminitis are initially found in the secondary epidermal lamellae (SEL) including lengthening and narrowing, developing tapered tips and with SELs angled more acutely to the primary epidermal lamellar axis.⁷⁰ Stretching of the lamellar epithelial cells is the earliest histological change observed after 6 hours of hyperinsulinemia and subsequent cellular changes include an accelerated cell death (apoptosis) and proliferation cycle.^{71,72} This cellular stretching indicates cytoskeletal disruption,⁷⁰ and deformation of the lamellae also explains how divergent laminitic rings can often appear before lameness.⁶⁹

It is less well established how hyperinsulinemia causes laminitis, with various theories having been disproven including glucose deprivation,⁷³ glucotoxicity,⁷⁴ matrix metalloprotease upregulation,⁷⁵ and increased blood flow-induced hyperthermia.⁷⁶ Current plausible theories include changes in intracellular insulin signaling resulting in endothelial dysfunction and mechanisms involving insulin-like growth factor 1 (IGF-1). In healthy animals, stimulation of insulin receptors initiates intracellular signaling processes via the so-called metabolic pathway, which result in nitric oxide-mediated vasodilation and GLUT4 translocation.⁷⁷ Blockade of this metabolic pathway in IR favors the alternative so-called mitogenic or mitogen-activated protein (MAP) kinase (or Ras ERK 1/2) pathway, which results in endothelin 1-mediated vasoconstriction, upregulation of cellular adhesion modules, and mitogenesis.⁷⁷ Support for a potential vascular mechanism linking IR and laminitis comes from studies of horses where an abnormal contractile response to insulin was observed in digital vessels and lamellar arteries in the presence of IR,^{78–80} and also increased endothelin-1 has been measured after insulin infusion in an ex vivo perfused limb model.⁸¹ However, research on vascular endothelial dysfunction provides a limited view of the intracellular events that occur during hyperinsulinemia. It is likely that multiple hormones, cytokines, or signaling molecules play a role and that the roles might be different in the lamellar epithelial cells and vascular endothelium. The IGF-1 receptor has received attention owing to its similarity with the

insulin receptor and the ability of high concentrations of insulin to activate it resulting in intracellular signaling through the MAP kinase pathway.⁸² The IGF-1 receptor is found on lamellar epithelial cells as well as endothelia, unlike the insulin receptor that is primarily located only on endothelial cells.⁸³ Studies of horses have shown clear evidence of upregulation of intracellular signaling downstream from the IGF-1 receptor both in response to dietary carbohydrate challenge and insulin infusion.⁸⁴ Of particular relevance was the observed activation of the downstream molecule RPS6, which disrupts cytoskeletal regulation resulting in a loss of cell stiffness or integrity that might explain the observed cellular elongation or stretching.⁸⁴

5.3 | Role of microbiome, diet, and gut homeostasis

The intestine generates different types of messages via hormones and afferent nerves that inform peripheral organs (liver, adipose tissue, brain) of nutritional status, which in response generate signals to modify energy storage or expenditure.⁸⁵ Factors such as changes in diet or EDCs leading to disruption of gastrointestinal homeostasis can therefore influence the metabolic status of the whole body.

The gut microbiota has been suggested as a driving force in the pathogenesis of metabolic disease and obesity in humans and other species.^{86,87} A small study of fecal microbiota in EMS and control horses showed less diversity in EMS horses with an increase in *Verrucomicrobia* members,⁸⁸ which has been suggested as microbial biomarkers for progression of glucose intolerance in humans.⁸⁹ Additionally, small changes in carbohydrate content in different cuttings of hay elicited measurable changes in equine hindgut streptococci 4 hours after meal feeding,⁹⁰ and supplementation with short-chain fructo-oligosaccharides alters microbial populations in different parts of the intestine.⁹¹

5.4 | Role of obesity

Obesity is no longer seen as a sole cause of EMS but rather a commonly associated feature that, when present, can exacerbate ID.^{92,93} A possible consequence of increased fat mass is dysregulation of adipokines, including leptin and adiponectin, as well as inflammatory mediators, which might impact glycemic control, inflammation, and cardiovascular function.⁹⁴

Adipocytes are the main site of leptin synthesis and fat mass appears to be the primary determinant of serum leptin concentration in the horse.⁹⁵ Leptin serves to relay signals to the brain indicating fat status and to maintain body condition by appetite suppression and increased energy expenditure during energy excess.⁹⁶ In some horses, leptin concentrations exceed those expected based on the amount of fat due to the presence of obesity-related leptin resistance, which might act to worsen the existing degree of obesity.^{95,96} Increased leptin concentrations correlate with hyperinsulinemia in ponies.¹²

Adiponectin is a further adipokine secreted exclusively from adipose tissue, which improves insulin sensitivity and reduces inflammation.⁹⁷ Adiponectin concentration is inversely related to fat mass and IR.⁹⁵ Decreased adiponectin concentrations were associated with mildly increased serum amyloid A and development of ID in horses fed a cereal-rich diet, although horses fed a fat-rich diet showed no evidence of ID and had normal adiponectin concentrations.⁶³

Several studies in horses have examined a possible role of adipose tissue in generating inflammation by releasing various pro-inflammatory cytokines. However, findings have been inconsistent, possibly reflecting differences between fat depots and individual variability, and the association of inflammation with ID and generalized or regional obesity remains unclear.^{24,93,98–105}

5.5 | Role of genetics

The expression of EMS is the result of a complex interaction between genetics and the environment. Although environmental factors including excessive nutrition have been linked to EMS, high planes of nutrition or changes in the pasture do not result in metabolic derangements and laminitis in all horses indicating the importance of underlying genetic influences.⁹² Horses with EMS are often considered “good doers” or “easy keepers,” and genes contributing to this phenotype are likely to be advantageous for survival in the wild during periods of famine by enhancing feed efficiency.¹⁰⁶ Initial research into the genetic components of EMS in a group of ponies found that the prevalence of laminitis was consistent with the action of a major gene or genes expressed dominantly, but with reduced penetrance attributable to sex-mediated factors, age of onset, and further epigenetic factors.⁶ More recently, genome wide association studies have been undertaken using Arabian horses, Welsh ponies, and Morgan horses, and several candidate genes were identified associated with relevant traits including height and insulin, triglyceride, and adiponectin concentrations.^{106–108} Nutritional status and body condition of the mare during pregnancy influences the foal in terms of reproductive, orthopedic, and metabolic responses later in life, probably related to epigenetic changes in utero.^{109,110}

6 | LABORATORY DIAGNOSIS

Among the various testing protocols for assessing laboratory markers of ID, analysis of blood samples to determine insulin concentration is a common feature. Several studies have reported marked differences in equine insulin values determined by different laboratory methods.^{111–115} Therefore, cutoff values generated in particular studies cannot be applied universally, and care should be taken to only directly compare results generated using the same insulin assay. Samples for glucose assay should be collected into tubes designed for preserving plasma glucose such as oxalate fluoride or sodium fluoride and, ideally, be chilled.

Different test procedures provide diverse information regarding aspects of ID (Figure 1), which might partly explain discordant results when various test procedures are compared.^{116–121} Knowledge about physiological principles of the test procedure is important to interpret results and to identify which component or components of ID are affected. In general, a complete assessment of ID can be achieved in a step-wise manner by combining multiple diagnostic tests.

6.1 | Pretest considerations

Acute stress can affect insulin and glucose concentrations via activation of the adrenocortical axis and by catecholamine release. It is advisable to minimize stress from transportation, environmental and

feeding management changes, pain from active laminitis, or excessive starvation before testing.^{122–125} Although the absence of feed intake might be expected to decrease insulin concentrations, fasting for as little as 6 hours can cause IR in horses and donkeys.^{122,126} Furthermore, postprandial glucose or insulin responses will be affected by gastric emptying, which in turn will be influenced by the presence or absence of ingesta in the stomach and small intestine and therefore feeding status should always be considered.

6.2 | Basal testing

6.2.1 | Insulin

An indication of ID can be based on finding resting (or basal) hyperinsulinemia.⁴ However, the use of fasting before measuring basal insulin is no longer recommended owing to low sensitivity for ID as well as the possible confounding effects of secondary IR induced by the fasting protocol. Measurement of insulin within 4–5 hours of grain feeding is also not recommended owing to lack of standardization of responses. Serum insulin concentrations measured in ponies 1–3 hours after coming off pasture could differentiate laminitis-prone individuals using a cutoff for insulin of 20 $\mu\text{IU/mL}$ using the Coat-a-Count radioimmunoassay (RIA).^{6,7} Resting insulin can also be measured under forage-fed conditions, although the effects of different forages and rates of consumption will influence results. In 112 ponies with free access to hay, a reference interval of 2.0–21.1 $\mu\text{IU/mL}$ was established with the Immulite 2000 chemiluminescent assay.¹²⁷ In another study, 6 normal ponies fed 0.25% BM forage as dry matter intake (DMI) had peak insulin values of <3.9 $\mu\text{IU/mL}$ when fed soaked hay and <19.8 $\mu\text{IU/mL}$ when fed dry hay using the same assay (Immulite 2000).¹²⁸ Haylage feeding was associated with higher peak insulin values in these normal ponies (up to 66.0 $\mu\text{IU/mL}$).¹²⁸ When forage of unknown quality is being fed, mild increases in resting insulin concentrations (20–50 $\mu\text{IU/mL}$) should be considered suspicious for ID and dynamic testing using OGT or OST is recommended (Equine Endocrinology Group: <https://sites.tufts.edu/equineendogroup/>. Accessed May 6, 2018).

6.2.2 | Glucose

Measuring resting plasma glucose in horses with suspected ID is generally uninformative although warrants inclusion for identification of occasional cases of *diabetes mellitus*.¹²⁹

6.2.3 | Triglycerides

Horses and ponies affected by EMS often suffer from dyslipidemia,^{12,130} and hypertriglyceridemia has been found to be a significant predictor of laminitis in ponies with cutoff values from 0.64 to 1.06 mmol/L (57–94 mg/dL).^{6,7} Given the relatively mild and inconsistent changes, however, this has not proved to be a reliable diagnostic test.

6.2.4 | Adipokines

Adiponectin is an adipose-derived hormone with antiinflammatory and insulin-sensitizing actions that is synthesized as monomers and secreted into the circulation as trimers, low-molecular-weight hexamers, and high-molecular-weight (HMW) multimers.¹³¹ In humans, HMW adiponectin is generally regarded as a more sensitive marker of metabolic disease than total adiponectin concentration,¹³² although the importance of total adiponectin is also supported.¹³³ In horses, both HMW and total adiponectin

are associated with obesity and ID,^{104,134} and low total concentrations are identified as a risk factor for future laminitis.¹¹ An immunoturbidimetric assay has recently been validated for total adiponectin in equine samples.¹³⁵ Leptin concentrations are useful in the prediction of laminitic episodes in ponies⁷ although they appear better associated with fat mass rather than ID in horses and therefore have the potential to mislead in EMS investigation.^{26,63,95}

6.2.5 | C-peptide

C-peptide is co-secreted with insulin in equimolar amounts.¹³⁶ In contrast to insulin, C-peptide is unaffected by the hepatic first pass effect and therefore provides a more accurate assessment of pancreatic secretion of insulin.¹³⁷ Increased C-peptide concentrations in response to oral and IV administered glucose have been described in horses using RIA.^{64,138} A commercially available ELISA is also described, which performed acceptably in horses.¹³⁸

6.2.6 | Incretins

Studies of the diagnostic usefulness of plasma incretin concentrations thus far have not offered adequate support for their employment as markers for ID and EMS, although some encouraging findings are reported for active GLP-1^{52,55,56,139} and GLP-2.⁵⁸

6.3 | Dynamic testing

Dynamic tests provide additional information on the relationship between insulin and glucose and are generally more sensitive than basal testing for identification of ID. Tests measuring responses to PO administered NSC more closely mimic the more complete sequence of glucose and insulin dynamics following food intake, whereas tests measuring responses to IV insulin, glucose, or both focus on tissue insulin sensitivity and beta cell responsiveness. In experimental and research settings, tests including the frequently sampled IV glucose tolerance test^{62,129,140} and the euglycemic hyperinsulinemic clamp^{116,118} are often used to investigate insulin and glucose regulation but are too complex and costly for routine clinical use.

6.3.1 | Oral challenge tests

Oral glucose test

In-feed oral glucose tests (OGTs) can be performed by offering glucose (or dextrose) powder mixed in small, low-glycemic meals,^{2,141,142} and post-glucose insulin concentration has been shown to be associated with the risk of developing laminitis in ponies being fed a high-NSC diet.¹⁴² Fasting overnight is recommended before the test, both to increase compliance with ingesting the test dose and to facilitate gastric glucose transit. Most frequently 0.5 or 1.0 g/kg body mass (BM) glucose powder is used. Peak plasma glucose occurs between 60 and 120 minutes after consuming the meal.¹¹⁷ The main limitation of the protocol is that palatability of the large glucose dose can be poor, and test results may be affected by ingestion time, gastric emptying, and intestinal absorption.^{143,144} However, a recently published dosage of 0.75 g/kg BM resulted in satisfactory results and increased acceptance by ponies.¹⁴⁴ Insulin concentrations regarded as indicative of ID, when measured at 120 minutes post-feeding, are >68 $\mu\text{IU/mL}$ for 0.5 g/kg BM glucose and >80–90 $\mu\text{IU/mL}$ for 1.0 g/kg BM glucose with Immulite 1000 chemiluminescent analysis (Equine Endocrinology

Group: <https://sites.tufts.edu/equineendogroup/>. Accessed May 6, 2018).^{141,145} In a study where 14 of 37 ponies developed laminitis while receiving a high-NSC diet, no pony developed laminitis that had resting insulin <8.5 μ U/mL and insulin <65.5 μ U/mL at 120 minutes following 1.0 g/kg glucose using the ADVIA Centaur chemiluminescent assay.¹⁴²

As an alternative, the OGT can be performed with 1.0 g/kg BM glucose dissolved in 2 L of water and administered via nasogastric tube as long as sedation or stressful restraint are not required.¹⁴⁶ The suggested cutoff value for this test protocol is 110 μ U/mL insulin at 120 minutes, using the equine optimized insulin ELISA.¹⁴⁶

Oral sugar test

The oral sugar test (OST) uses a specific corn syrup (Karo Light Corn Syrup; ACH Food Companies, Inc, Oakbrook Terrace, IL) at a dosage of 0.15 mL/kg BM PO via dosing syringe.¹¹⁹ Although pretest fasting has not always been found to affect results,¹⁴⁷ it is advised that horses should be fasted for between 3 and 12 hours before the OST.^{122,123} This might be accomplished by offering a reduced amount of hay (eg, 0.2–0.4 kg per 100 kg BM) the night before the test. Blood sampling to measure insulin response is recommended at between 60 and 90 minutes after corn syrup (Karo Light Corn Syrup; ACH Food Companies, Inc) administration. Insulin concentrations >60 μ U/mL post-dosing were initially used to indicate ID using RIA (Millipore Human RIA),^{141,148} although a lower cutoff of >45 μ U/mL was recommended more recently using the same assay (Equine Endocrinology Group: <https://sites.tufts.edu/equineendogroup/>. Accessed May 6, 2018). A higher dosage of 0.25 mL/kg BM corn syrup (Karo Light Corn Syrup; ACH Food Companies, Inc) was suggested to improve diagnostic value with a cutoff of >30 μ U/mL between 60 and 90 minutes using Coat-A-Count RIA.¹⁴⁹ An even higher dosage of 0.45 mL/kg BW corn syrup (Karo Light Corn Syrup; ACH Food Companies, Inc) could provide higher sensitivity for ID with a value of >110 μ U/mL measured by RIA (Insulin CT, MP Biomedical) at 60 minutes successfully differentiating 5 previously laminitic ponies from 3 ponies with no history of laminitis.¹⁴⁷ Cutoff values have also been determined for insulin concentrations measured with other assays, and results from the higher dose OST in 35 ponies with no history of laminitis indicated cutoffs between 60 and -90 minutes post-dosing of 40 μ U/mL using the Immulite 1000 and 63 μ U/mL using the Immulite 2000xpi chemiluminescent assays (A. E. Durham, unpublished data).

A further OST using commercially available Scandinavian glucose syrup (Dan Sukker Glykossirap; Nordic Sugar A/S, Copenhagen, Denmark) has been described.¹⁵⁰ A dosage of 0.2 mL/kg BM is comparable to corn syrup at 0.15 mL/kg, although reference ranges have not been established to date.

Finally, horse compliance might be improved by using a grain-based diet as a carbohydrate challenge rather than glucose, with comparable insulin responses and prediction of laminitis risk.^{142,144} However, the type of grain, consumption time, variable gastric transit, and absorption could still confound test results.

6.3.2 | Intravenous challenge tests

Parenteral delivery of exogenous glucose, insulin, or both has the advantage of decreasing variability associated with gastrointestinal

transit and absorption but also omits some possibly important elements of ID including incretin effects. Nevertheless, such tests allow focus on specific elements of ID such as IR and have been successfully used to diagnose and monitor EMS in clinical and research settings.^{151,152}

Insulin response test (IRT)

The insulin response test (IRT) measures the glycemic response to exogenous insulin, directly assessing insulin-dependent glucose uptake and insulin sensitivity. Forage is made freely available during the test to reduce the risk of clinical hypoglycemia.¹⁵³ In normal horses, blood glucose will decrease to <50% of the baseline concentration within 20–30 minutes after 0.02–0.125 IU/kg BM neutral (regular) insulin IV and then return back to baseline levels within 2 hours.¹⁵⁴ In horses with IR, the blood glucose concentration will remain higher and return to baseline sooner. An abbreviated protocol is described with glucose measured before and 30 minutes after 0.1 IU/kg BM neutral insulin IV, followed by dextrose administration, or a small feed, after 30 minutes to prevent hypoglycemia.¹⁵⁵

Combined glucose insulin test

The combined glucose insulin test (CGIT) is based on injection of 150 mg/kg BM glucose IV, directly followed by 0.1 IU/kg BM neutral (regular) insulin IV.¹⁵⁶ In a shortened protocol, both insulin and glucose are measured in the basal sample and after 45 and 75 minutes.¹⁵² Typical healthy horses show a biphasic blood glucose curve starting with hyperglycemia, followed by a negative phase in which glucose drops below the initial baseline value. Glucose should normally then increase back to baseline concentrations within 45 minutes. Insulin concentration should be under 20 μ U/mL both at baseline and at 75 minutes, and remain <100 μ U/mL at 45 minutes when analyzed with the Coat-A-Count RIA.¹⁵⁶ Hyperinsulinemia and a delayed return to baseline glucose indicate ID. The CGIT is generally well tolerated although hypoglycemia can occur and tested horses should be closely monitored and additional glucose injections or a small feed should be readily available.

6.4 | Testing for PPID

There are similarities between EMS and a subset of animals with PPID in terms of predisposition to laminitis and the presence of ID.^{157,158} and, furthermore, the 2 conditions can coexist. Thus, testing for PPID using basal ACTH concentrations or ACTH response to exogenous thyrotropin-releasing hormone (TRH) should be considered in horses with ID, laminitis, or both and especially those that are greater than 10 years of age.¹⁵⁹ Combined testing for PPID and ID with the TRH stimulation test and OST has been recently studied. When TRH stimulation testing is performed after PO administration of corn syrup, post-stimulation ACTH concentrations are significantly lower and, therefore, this order of combination testing is not recommended.¹⁶⁰

6.5 | Key laboratory testing recommendations

- The specific methodology used to quantify analytes such as insulin has a marked effect on results and should always be considered, especially when considering diagnostic criteria from published studies.

- The most useful and practical tests for routine assessment of the various manifestations of ID include resting (not fasting) insulin, the OGT or OST, and the IRT or CGIT.
- Interpretation of the test results requires a good understanding of the test selected.
- A subset of animals with PPID have ID, and EMS and PPID can coexist, thus concurrent testing for PPID should be considered in all horses over 10 years of age.

7 | MANAGEMENT

7.1 | Dietary energy restriction

Nutritional strategies for management of obesity primarily rely on energy restriction through limiting the total DMI. In general, grains or cereal-based complementary feeds, fruit, or vegetables such as carrots, apples, or treats should be excluded from the diet because of their high NSC content. Likewise, high-fat feeds should be avoided in obese horses because of their high energy contents.

Progressive BM losses by energy restriction improve insulin regulation in obese and ID horses and ponies.^{8,68,104,152,161–164} There is debate about the optimal degree of restriction owing to concerns about not meeting minimum roughage requirements.¹⁶⁵ In general, daily allowance of a mixed species grass hay-based diet of 1.25%–1.5% of actual BM as DMI, or 1.4%–1.7% of actual BM as fed, is recommended, typically corresponding to a digestible energy (DE) intake of 64%–94% of maintenance requirements.^{8,104,165,166}

There is considerable individual variability in proportional weight losses among horses subject to dietary restriction independently of variables such as their diet, ID, morphometric measures, or body fat content, leading to the categorization of individuals as either sensitive or resistant to weight loss.⁸ In horses resistant to weight loss, a further forage restriction to as little as 1.0% actual BM as DMI, or 1.15% actual BM as fed, should be considered if appropriately monitored.

The nutrient composition of the forage should be determined where possible,¹⁶⁷ although this seems to be performed rarely in practice.¹⁶⁸ Hays with low NSC content (<10%) are recommended to limit insulin responses,¹⁶⁹ although moderate (12%) or high (18%) NSC content in hay had no long-term effect on serum insulin concentrations in obese Arabian geldings in one study.¹⁷⁰ Haylage is often presumed to have low NSC owing to fermentation, although insulinemic responses to haylage are greater than to hay of an equivalent NSC content.¹²⁸ This, along with frequently greater palatability of haylage, means that it is not recommended for feeding horses with ID.

Soaking reduces the glycemic and insulinemic responses to hay and haylage fed to both normal and ID ponies^{128,171} and is recommended for horses with ID, especially those demonstrated to have abnormal responses to oral carbohydrate challenges. Soaking hay for 7–16 hours at ambient temperature decreases nutrients including water-soluble carbohydrates by 24%–43% and is associated with more than double the losses of BM compared to feeding the equivalent amount of dry hay.¹⁶⁵ However, there are concerns over microbial growth during a long soaking process in warm or tepid water unless the hay is subsequently steamed¹⁷² and therefore limiting to a 1- to

2-hour soak is recommended in warm conditions. As forages can be low in protein, and mineral and vitamin leaching occurs after soaking, these nutrients must be balanced by supplements to cover requirements.^{165,173} Increases in plasma creatinine was found in one study of dietary restriction as a result of muscle catabolism due to a deficient protein intake.¹⁶⁴

Dry matter intake is increased on pasture, at least when offered ad libitum,¹⁷⁴ and high NSC pasture has been shown to exacerbate hyperinsulinemia in ponies.⁶ Restricting grazing time alone has a limited effect on DMI and can result in rapid consumption with over 0.9% BM as DMI having been recorded in just 3 hours of time at pasture.^{175,176} Grazing muzzles reduce DMI to 77%–83% of grazing without a muzzle¹⁷⁷ and can have the added benefits of increasing foraging time and exercise. During the initial 6–12 weeks of dietary restriction in animals with ID, pasture access should be prevented as even partial access is difficult to quantify in terms of DMI. However, successful long-term management of EMS cases can still include some grazing provided that ID is under control. In this respect, ID is best assessed by the insulin response to PO administration of carbohydrates or after grazing.¹⁵²

The use of dietary supplements to facilitate BM losses or to improve ID is popular, but their efficacy remains questionable or unproven. Supplements including magnesium, chromium, and short-chain fructooligosaccharides have received support based on some evidence of improved insulin regulation,^{178–180} although other studies have not confirmed these positive effects.^{151,181} Little benefit has been shown for other supplements including cinnamon,¹⁸² L-carnitine,¹⁸³ and Psyllium,¹⁸⁴ although some promising effects are reported for a feed enriched with *Spirulina platensis* algae¹⁸⁵ and the wheat bran protein aleurone.¹⁸⁶

7.2 | Welfare considerations

Safe rates of BM loss are not well defined. Although abrupt feed restriction resulting in loss of approximately 1% BM weekly was not associated with hypertriglyceridemia in a study of Welsh ponies,¹⁶⁴ more rapid BM losses have been associated with increases in serum triglycerides and non-esterified fatty acid concentrations, reflecting increased lipolysis.^{166,183} Furthermore, quite considerable variation in individual sensitivity or resistance to weight loss can occur, in addition to effects of variation in hay quality.^{8,165} Consequently, energy restriction should be targeted toward achieving 0.5%–1.0% BM losses per week and carefully monitored during restriction to ensure targets are reached but not exceeded. There is rarely a need to institute abrupt diet restriction, and this can generally be phased in over a week or 2.

Attempts to extend feeding time during feed restriction are ideal for the animal's health and welfare.¹⁶⁴ As straw has a lower energy content than hay, DMI can be increased to >1.25% BM, thereby increasing feeding time. In one study, a mixture of alfalfa, hay, and straw was offered without any negative clinical consequences during a 17-week weight loss program in ponies.¹⁶³ Although other studies are lacking, gradual introduction of straw in exchange for hay at a rate of up to 30% of total forage can be recommended to allow increased DMI with little effect on DE intake. Monitoring fecal output to detect early signs of colon impaction is advisable after introduction of straw.

During feed restriction to a DMI of 1.0% BM in horses and ponies, feeding from a hay net compared to feeding from the stall floor resulted in extension of hay intake time from 120 to 193 minutes.¹⁷⁵ Dynamic feeding systems have been designed by applying time-dependent cycles with controlled hay access to provide a combination of exercise and extension of feed intake while improving BM losses.¹⁸⁷ A possible consequence of restricting DMI is ingestion of bedding such as straw, wood shavings, or paper,¹⁸⁸ and consequently, rubber matting in stables might be considered in some cases during energy restriction. The impact of dietary restriction on the incidence of gastric ulceration and behavior should also be considered. Both these concerns were examined in a study of 16 weeks' dietary restriction in Shetland ponies where no effect on gastric ulceration was found.¹⁶⁶ The same study suggested an increase in coprophagy during the period of dietary restriction, whereas other studies have found feed restriction to be associated with lethargy.^{189,190}

7.3 | Key dietary recommendations

- An ideal target for weight loss in obese horses is between 0.5% and 1.0% BM losses weekly.
- This may be achieved with a forage-based ration totaling 1.4%-1.7% BM as fed, or in exceptional cases that appear weight loss resistant, as little as 1.15% BM as fed.
- Forage with NSC <10% is recommended to limit postprandial insulin responses in horses with ID and soaking may be required to achieve this in many instances.
- Ensuring adequate protein, vitamins, and minerals is important via a ration balancer supplement.

7.4 | Exercise programs

Exercise improves insulin sensitivity and reduces inflammation in people, even in the absence of weight loss.^{191,192} A similar antiinflammatory effect has also been observed in ponies undergoing low intensity training (5 minutes trotting per day for 14 days) with a reduction in serum amyloid A and normalization of serum haptoglobin in previously laminitic ponies.¹⁹³ However, based on the evidence from human studies, exercise intensities required for improving insulin sensitivity may be higher than are often undertaken, which may explain the variable success of programs that used lower intensities of exercise.¹⁹⁴ Low-intensity exercise in young- to middle-aged horses and ponies should be producing HRs of 110-150 beats per minute (BPM) (50%-70% HR_{max}) and moderate intensity 150-190 BPM (70%-90% HR_{max}). As a guide, for inactive to lightly exercised horses, fast trotting on a lunge elicits HRs of around 100-110 BPM and canter 120-160 BPM whether ridden or unriden.¹⁹⁵

An increase in insulin sensitivity has been found for several days following 7 days of endurance training in healthy Standardbred horses at 55% VO_{2max} (70% HR_{max} or 150 BPM) for 45 minutes¹⁷ with similar beneficial findings for low-to moderate-intensity exercise in other studies of healthy and obese horses.^{18,19} Swimming healthy Thoroughbred horses in a moderate intensity exercise program for a month (HRs 160-180 BPM for 60 minutes per day) decreased basal and dynamic plasma insulin concentrations.¹⁹⁶

However, not all studies have found exercise to improve basal insulin or insulin dynamics,¹⁹⁷ and lower levels of exercise have frequently had disappointing results. Only short-term improvements in insulin sensitivity were found after 7 days of 30 minutes light exercise (mean HR 130 BPM) in obese mares,¹⁹⁸ and only a marginal improvement in OGT responses was seen after 6 weeks of training obese ponies (5 days a week for 9 minutes trot and canter, HR <140 BPM), although their improvements were maintained over 6 weeks deconditioning.¹⁶¹ Insulin sensitivity was not improved during an exercise program of 2 weeks of 30 minutes slow trotting for 4 days/week and 2 weeks of 30 minutes trotting for 2 days per week and 20 minutes slow cantering plus 10 minutes trotting for 2 days/week.¹⁹⁷

7.5 | Key exercise recommendations

Exercise recommendations are opinions extrapolated from medical research and clinical experience; relative gait and HR ranges are based on horse and pony exercise physiology research.

- Exercise recommendations will depend on lamellar stability and cannot be applied to horses with current or recent laminitis. All exercise should be increased gradually based on the horse's baseline fitness level and with careful monitoring in case of deterioration of lamellar stability especially in horses with previous laminitis.
- In nonlaminitic horses with ID, minimum recommendations are low-to moderate-intensity exercise (canter to fast canter, ridden or unriden; or HRs 130-170 bpm) for >30 minutes, >5 times per week.
- In previously laminitic horses with recovered and stable hoof lamellae, minimum exercise recommendations are low-intensity exercise on a soft surface (fast trot to canter unriden; or HRs 110-150 bpm) for >30 minutes, >3 times per week, while carefully monitoring for signs of lameness.

8 | PHARMACOLOGIC AIDS

Metformin hydrochloride is commonly prescribed for managing ID in equids although it is only licensed for use in humans. Dosages range from 15 to 30 mg/kg q8-12h PO, and the drug should ideally be administered 30-60 minutes before feeding. An initial study administered metformin (15 mg/kg PO q12h) to 18 ponies and horses with ID and reported that basal insulin concentrations decreased over time.¹⁹⁹ However, the oral bioavailability of metformin is poor in equids,²⁰⁰ and it does not have systemic effects on insulin sensitivity.²⁰¹ Instead, metformin has a direct effect on the enterocyte in other species,²⁰² and decreases enteric glucose absorption and consequently the insulin response to an OGT in horses and rats,^{203,204} providing a possible explanation for the observed beneficial actions of metformin on insulin concentrations in the absence of systemic absorption. Indeed, response to metformin can be evaluated by performing an OST or OGT 30-60 minutes after drug administration to assess the benefits in the individual patient,²⁰³ or by comparing insulin concentrations 2 and 4 hours after feeding with and without medication.

Levothyroxine might be prescribed for equids with increased adiposity to accelerate weight loss through increasing the metabolic rate, but diet and exercise changes should ideally be implemented at the same time. Administration of levothyroxine to healthy horses of 500 kg BM at dosages between 24 and 96 mg per day PO for up to 48 weeks was well tolerated, BM decreased, and insulin sensitivity increased.²⁰⁵ Levothyroxine treatment in horses with EMS has beneficial effects on BM and neck circumference after 48 mg levothyroxine/day PO for 6 months and then 72 mg levothyroxine/day for 3 months.²⁰⁶

There is a product available for use in horses in the United States (Thyro L; LLOYD, Inc, Shenandoah, Iowa) at a dosage of 0.1–0.15 mg/kg levothyroxine sodium once daily PO until an appropriate body condition is attained or for a maximum of 6 months. Horses are weaned off levothyroxine at the end of the treatment period by decreasing the dose by half for 2 weeks and then a quarter for 2 weeks. In Europe, use of levothyroxine in equids requires prescription of products licensed in other species.

Pioglitazone is a thiazolidinedione antidiabetic drug that is prescribed for the management of type 2 DM in humans. This drug is not routinely used for managing ID in horses, as results from early equine studies were largely disappointing^{207,208}; however, findings from a recent study examining effects of pioglitazone (2 mg/kg PO q24 h for 28 days) on OST results and serum HMW adiponectin concentrations in healthy horses and ponies are more encouraging.²⁰⁹

Pergolide is a dopamine receptor agonist licensed in several countries for the treatment of PPID in horses (Prascend; Boehringer Ingelheim Vetmedica, Inc, Ingelheim, Germany). Medical management of PPID with pergolide typically improves insulin regulation in those horses affected by ID and it has been further proposed that pergolide might have an independent effect on insulin dynamics in horses. One study treated horses with clinical signs of EMS with 1 mg pergolide/day for 8 weeks and found improved OST results (D. McFarlane, personal communication), although it is difficult to rule out early PPID in those horses with EMS, so additional studies are required to confirm any specific effect of pergolide on ID. Several dopamine agonists improve insulin regulation and suppress insulin concentrations in other species,²¹⁰ although no beneficial effect of cabergoline on ID in horses has been found.²¹¹

Sodium-glucose co-transporter 2 (SGLT2) inhibitors target receptors in the proximal tubule of the kidney to increase glucose loss in the urine.²¹² Preliminary studies have been performed to assess the safety and efficacy in horses, but further work should be done before more widespread use.²¹³ In humans, SGLT2 inhibitors are administered once daily as tablets and hypoglycemia and urinary tract infections are the most common adverse events reported.

Sweet taste receptor (T1R2/3) inhibitors have been used to reduce the insulin and glucose responses to oral carbohydrates in other species, and evidence of some minor beneficial effects has been shown recently in horses as well.²¹⁴

8.1 | Key pharmacologic recommendations

- Drug treatment of EMS should never be used as a substitute for diet and exercise interventions.

- Because metformin appears to blunt postprandial increases in blood glucose and insulin, it may be useful for horses with severe ID while management changes are implemented, and in animals that remain insulin dysregulated even when managed optimally.
- Levothyroxine may be used in weight loss-resistant cases alongside dietary control and exercise.
- Where PPID has been diagnosed, pergolide treatment is recommended to minimize the effects of PPID on ID.

9 | MONITORING AND PREVENTION

9.1 | Laminitis detection

All horses with EMS must be monitored frequently for the earliest clinical signs of laminitis, which are often seen when the horse is turned in tight circles on a hard surface or transitions from soft to hard ground. Digital pulse intensity increases as laminitis progresses. However, some equids have hoof changes consistent with lamellar damage without exhibiting lameness.⁶⁹ In these cases, divergent hoof rings ("founder lines") might be seen on the hoof wall or widening of the white line on the solar surface. Third phalanx remodeling, displacement, or rotation might be detected in the same horses when radiographs are taken of the feet. Ideally, evaluations should be performed every 6–12 months to reassess the risk of laminitis. The minimum database for each visit includes an updated diet and exercise history, physical examination and body condition score, visual inspection of hooves for signs of laminitis, and endocrine tests (eg, OST). It is also crucial that preventive and corrective farriery is coordinated alongside veterinary care.²¹⁵

9.2 | Obesity control

Although diet and exercise recommendations might appear relatively straightforward, they can often be limited by poor compliance from horse owners and other practical barriers to implementation.²¹⁶ Key factors in EMS management are both the tailoring of the program to individual owners' situations and monitoring the effect.²¹⁷ A tendency for owners of obese horses to underestimate their horse's condition has been identified by several studies.^{27,30,32} Various reasons have been proposed to explain the apparent lack of recognition of obesity including lack of owner education.³⁹ However, it should also be acknowledged that the high prevalence of equine obesity can lead to habituation and acceptance of the status as apparently normal. Additionally, perceived criticism and peer pressure from owners of overweight horses stabled on the same premises can present a barrier to other owners wishing to implement fat loss programs.²¹⁶ Continual overt veterinary support and education are crucial to promote the success of advised management changes.

Body mass monitoring on a weighbridge is ideal although tapes or commercial applications, which consider belly, girth, and rump width are useful alternatives.^{164,218} Body condition scoring to monitor success has some limitations because of the nonlinear relationship of total body fat with BCS when BCS is greater than 7/9,²¹⁹ and variable reported changes in BCS after 6–12 weeks of energy restriction.^{104,151,164} In the

first week of energy restriction, higher BM losses are expected because of reduced gut fill after transition to restricted DMI^{164,183} and beyond the first 12 weeks of dietary restriction, the same level of restriction, even if adjusted for BM, might not have the same effect because of adaptive suppression of resting metabolic rate.⁸ Where this is the case, the level of dietary restriction may need to be increased or metabolic rate increased, for example, by implementing an exercise program.

9.3 | Endocrine monitoring

Body mass reduction is expected to improve ID,^{104,152,164} and laboratory testing is recommended to support the weight loss program and to confirm the degree of success in improving ID. The indication for dietary control should always be based on the degree of ID as well as BM, especially when used to guide return to pasture. For example, a horse with rapid improvements in ID might be able to resume restricted grazing relatively quickly and be maintained on long-term minor restrictions with some seasonal changes in BCS permitted. In contrast, a horse with continued marked ID might require low NSC feeding and maintenance irrespective of changes in BM. Ideally, monitoring should include an OST or OGT or simply the insulin response to the prescribed feed (eg, an insulin sample taken 2 hours after the morning feed or 2 hours after being turned out on to pasture) to allow evaluation of the requirement for continued low NSC intake. The regular monitoring of serum TG concentrations during the weight loss program helps to detect hyperlipemia owing to a negative energy balance, especially in pregnant animals or in miniature breeds, Shetland ponies, and donkeys.

9.4 | Key monitoring recommendations

- Monitoring and support are crucial elements of EMS management because of poor compliance rates.
- Initial veterinary reexaminations should be performed monthly after starting dietary restriction and then less frequently (3-12 monthly intervals) once good progress is made.
- Success should be judged on the basis of retesting for ID (especially using oral carbohydrate challenge tests) and not simply BM losses.

CONFLICT OF INTEREST DECLARATION

The authors provide the following declarations:

A.E. Durham is employed by the Liphook Equine Hospital that offers a commercial diagnostic service including endocrine testing of horses and has received travel expenses from Boehringer Ingelheim Vetmedica for meetings related to Equine Metabolic Syndrome.

N. Frank has received financial compensation for consultation on study design for Boehringer-Ingelheim Vetmedica, Inc. and Kindred Biosciences, Inc. Boehringer-Ingelheim Vetmedica, Inc. has also supported travel and accommodation expenses for Equine Endocrinology Group meetings.

C.M. McGowan is employed by the University of Liverpool which has received funding for research projects and consultancy related to Equine Metabolic Syndrome from Boehringer Ingelheim Vetmedica.

K. Feige is employed by the University of Veterinary Medicine, Hannover which has received funding for research grants related to Equine Metabolic Syndrome from Boehringer Ingelheim Vetmedica.

K. Fey is employed by the Justus-Liebig-University in Giessen/Germany and has received fees for consultancy, presentations as well as travel expenses from Boehringer Ingelheim Vetmedica for subjects related to equine endocrine diseases.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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