

## Review



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# Equine metabolic syndrome

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**Laminitis is one of the most common and frustrating clinical presentations in equine practice. While the principles of treatment for laminitis have not changed for several decades, there have been some important paradigm shifts in our understanding of laminitis. Most importantly, it is essential to consider laminitis as a clinical sign of disease and not as a disease in its own right. Once this shift in thinking has occurred, it is logical to then question what disease caused the laminitis. More than 90 per cent of horses presented with laminitis as their primary clinical sign will have developed it as a consequence of endocrine disease; most commonly equine metabolic syndrome (EMS). Given the fact that many horses will have painful protracted and/or chronic recurrent disease, a good understanding of the predisposing factors and how to diagnose and manage them is crucial. Current evidence suggests that early diagnosis and effective management of EMS should be a key aim for practising veterinary surgeons to prevent the devastating consequences of laminitis. This review will focus on EMS, its diagnosis and management.**

EQUINE metabolic syndrome (EMS) has been defined as the presentation of a phenotype of obesity, insulin resistance and laminitis or a predisposition to laminitis in equids (Frank and others 2010). Obesity is defined as increased regional (eg, cresty neck) or generalised adiposity. Insulin resistance is characterised by basal hyperinsulinaemia and/or an excessive insulin response to intravenous or oral glucose challenge (insulin dysregulation). Laminitis is defined as that occurring in the absence of recognised inflammatory causes, such as grain overload, colic and metritis, and non-weight bearing causes such as fracture.

It is important to look at what each of these components really mean in equids. Obesity is a risk factor, insulin resistance is central to the pathophysiology of the disease while laminitis is the resultant clinical effect. Obesity on its own does not mean a horse has EMS; demonstration of insulin resistance and laminitis (or a predisposition to laminitis) is required to demonstrate EMS.

## How common is EMS?

Despite a growing interest in EMS there is little epidemiological data on its prevalence, possibly due to the difficulties in defining a clinical case. The prevalence of the individual components of EMS

are, however, easier to evaluate. Obesity prevalence is estimated at between 19 and 40 per cent in domesticated populations (Wyse and others 2008, Stephenson and others 2011, Thatcher and others 2012), while hyperinsulinaemia is found in between 22 and 29 per cent of susceptible equine populations (Muno and others 2009, Morgan and others 2014b). The prevalence of laminitis solely attributable to EMS is unknown, since studies tend to report all forms of laminitis together with a wide variation in prevalence estimates (1.5 and 34 per cent) (Wylie and others 2011). Endocrinopathic laminitis, which encompasses EMS and pituitary pars intermedia dysfunction (PPID), has been reported to account for up to 89 per cent of primary laminitis cases in one hospital; 66 per cent of these were diagnosed with EMS (Karikoski and others 2011). It is clear from these studies that the components of EMS are highly prevalent, resulting in a large number of 'at risk' individuals.

## The role of obesity in EMS

Obesity is defined by the World Health Organization as abnormal or excessive fat accumulation that may impair health. Obesity has been associated with increased morbidity and mortality in horses (Geor 2008) and is increasingly recognised as a welfare concern (Owers and Chubbock 2013).

Obesity is the main known risk factor for EMS. Adipose tissue is an active endocrine organ secreting adipokines (eg, leptin and adiponectin) and adipose-derived cytokines (eg, tumour necrosis factor [TNF] $\alpha$ , interleukin [IL]-1) which can have adverse local and systemic effects. Although the precise mechanisms by which insulin resistance develops in obesity has yet to be elucidated, a substantial body of work on the subject in rodent models and people has shown that when adipose stores are high, a combination of local and remote inflammation, dysregulated local glucocorticoid metabolism, oxidative damage, lipid overspill and alterations in the release and action of adipokines combine to impair insulin signalling within fat and muscle such that organism-wide insulin resistance develops (Kahn and Flier 2000, Kahn and others 2006, Tomlinson and others 2008). There is also evidence in people that different adipose deposits have different metabolic functions, such that the pattern of obesity may be as important as the degree of obesity; for example, central obesity in people is strongly associated with an increased cardiovascular risk (Kannel and others 1991).

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FIG 1: Obesity (a) is the main known risk factor for equine metabolic syndrome, and in horses excess visible fat deposition occurs most commonly in the region of the neck crest (b) and rump (c)

A small number of studies have attempted to tease out the possible role of fat in the development of EMS (Burns and others 2010). In horses, excess visible fat deposition occurs most commonly in the region of the neck crest and rump (Fig 1). Some researchers have suggested that neck crest adipose tissue is more active than omental adipose in horses, but the data are not conclusive (Burns and others 2010).

### Insulin resistance and its role in EMS

Insulin resistance is the failure of tissues to adequately respond to circulating insulin and thus control the blood glucose concentration. Insulin resistance can be classified as compensated or uncompensated. Compensated insulin resistance refers to a state in which the pancreas responds to peripheral resistance by producing more insulin in combination with decreased insulin clearance, resulting in hyperinsulinaemia (De Graaf-Roelfsema 2014). Uncompensated insulin resistance refers to pancreatic exhaustion, whereby the pancreas is no longer able to produce enough insulin and glucose control is poor; that is, type 2 diabetes. Horses most commonly have compensated insulin resistance and rarely develop pancreatic exhaustion and type 2 diabetes (Durham and others 2009).

Compensated insulin resistance is a key feature of the pathophysiology of EMS. Affected horses and ponies demonstrate resting hyperinsulinaemia and/or the development of marked hyperinsulinaemic responses to carbohydrate challenge (intravenous or oral glucose challenge), collectively described as insulin dysregulation (Frank and Tadros 2014). The role of the enteroinsular axis and the direct effects of ingested carbohydrates on intestinal incretin production are also under increasing scrutiny as an important part of the pathophysiology and a potential diagnostic tool (De Graaf-Roelfsema 2014). In addition, hyperinsulinaemia itself may also drive or worsen insulin resistance, possibly by down-regulation of insulin receptors or alterations in clearance (Del Prato and others 1994, Shanik and others 2008).

Sustained hyperinsulinaemia is associated with many adverse effects of metabolic syndrome in people, predominantly related to

vascular dysfunction, and remains central to the pathophysiology of resultant cardiovascular disease. In horses, basal unfasted hyperinsulinaemia has been associated with susceptibility to laminitis in pastured ponies (Treiber and others 2006), and a predictor of incipient pasture-associated laminitis in ponies (Carter and others 2009). Laminitis could be predicted by any three of the following four criteria: a body condition score of 7 or more, a cresty neck score of 4 or more, basal insulin over 32  $\mu\text{iu/ml}$ , leptin of over 7.3 ng/ml; however basal insulin alone (>32  $\mu\text{iu/ml}$ ) predicted laminitis as accurately as the combination of criteria (Carter and others 2009). Experimentally, laminitis can be induced by insulin infusion inducing hyperinsulinaemia for an average of 48 to 55 hours (Asplin and others 2007, De Laat and others 2010), or by the induction of hyperglycaemia along with a lower concentration of endogenous insulin (200  $\mu\text{iu/ml}$ ) over a similar time period (De Laat and others 2012).

### Laminitis and EMS

Laminitis can be viewed as the vascular dysfunction consequence of metabolic syndrome in the horse (Katz and Bailey 2012). The primary insult to the hoof in EMS is most likely due to alteration in the form and function of the vasculature, rather than inflammation, in contrast with laminitis secondary to systemic inflammatory response syndrome. How this primary insult occurs is unclear, but high insulin concentrations may affect blood vessel tone, resulting in an altered blood supply to the hoof (Venugopal and others 2011, 2014, Keen and others 2012). There is also some evidence to suggest that insulin may have a direct effect on the epidermal cells of the lamellar tissue via insulin-like growth factor signalling pathways (De Laat and others 2013).

Histological studies have shown that naturally occurring endocrinopathic laminitis differs from that reported in inflammatory models, in particular that the rapid devastating disruption of the basement membrane seen in inflammatory models does not occur in endocrine models or naturally occurring disease (Karikoski and others 2014a, b). Although elongation, altered keratinisation and disruption of the lamellar-hoof wall junction remains the most severe outcome, most cases of endocrinopathic laminitis were associated with a prolonged subclinical phase with histological and gross changes (predominantly laminitic rings and separation of the white line and cap horn production) without a clinical history of pain (Karikoski and others 2014a). Horses and ponies with hyperinsulinaemia and a relatively recent bout of laminitis showed gross and histological lesions consistent with laminitis indistinguishable from those that had laminitis for years. However, breed- and age-matched control ponies and horses without hyperinsulinaemia had no lesions (Karikoski and others 2014a). This supports the theory that equids with underlying metabolic syndrome can have painful or non-pain-



ful bouts of laminitis for many years before diagnosis and that, if underlying metabolic syndrome remains unmanaged, recurrence of laminitis is likely. Other research has shown that horses that have had laminitis previously are more likely to have further bouts (Wylie and others 2013), which emphasises the notion that diagnosis and management of EMS before laminitis develops is key to preventing chronic, recurrent laminitis.

### Genetic predisposition in EMS

Published cases of EMS have largely occurred in British native breeds. This is supported by Finnish research that found that 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 (Karikoski and others 2011). Breed differences in insulin sensitivity have been demonstrated, where ponies and Andalusian-cross horses showed reduced insulin sensitivity compared to standardbred horses (Bamford and others 2014), and it may be that their metabolic differences solely account for the predisposition to EMS. It is likely that EMS is a multifactorial disease with complex genetic and environmental interactions at play (McCue and others 2015).

### Diagnosing EMS Clinical evaluation

A tentative diagnosis of EMS may be made in horses that are clinically obese, of a predisposed breed and suffering from laminitis. Obesity and history of laminitis, or hoof changes indicative of earlier episodes should be documented and insulin resistance confirmed. The challenge remains to diagnose EMS before the onset of laminitis. To achieve this, evaluation of insulin regulation in susceptible breeds, especially those that are obese, offers essential information for assessing laminitis risk, monitoring progress and guiding intervention (Karikoski and others 2014b, Morgan and others 2014a).

Body condition scoring (BCS) systems are the most frequently used method of defining equine obesity given the limited availability of weigh bridges and difficulties in defining obesity in terms of bodyweight in a species with so much breed variation. A score of 4 or 5 out of 5 (Carroll and Huntington 1988) or 7 or more out of 9 (Henneke and others 1983) are often used as cut-offs for defining equine obesity. However, these scoring systems have significant limitations in true estimation of body fat, with horses with BCS over 5/9 having a nonlinear relationship between BCS and total body fat (Dugdale and others 2011). Irrespective of the scoring system, there are also limitations in owner application (Stephenson and others 2011), and owners have been shown to underestimate the BCS of their animals even using very simple systems (Ireland and others 2012). Simple, objective and repeatable adjunctive tools, such as body girth measurements, may offer a more accurate estimation of body fat in moderate-to-obese horses (Dugdale and others 2011), and may be more widely used in the future. Assigning a score to the neck crest can also be useful in recognising horses with regional obesity (Carter and others 2009).

It is very important that veterinary surgeons recognise subclinical laminitis, but this can be challenging. Visible changes to the hoof wall, such as divergent or 'laminitic' rings, may indicate previous episodes of laminitis, and are closely associated with histological lesions (Karikoski and others 2014b). Reduced concavity of the sole, dropped soles, a widened white line and presence of cap horn are all other potential indicators of subclinical laminitis. Farriers may be able to pick up these horn changes more readily than owners.

If PPID is suspected (in horses of  $\geq 15$  years of age, clinical signs may include hypertrichosis/delayed haircoat shedding, abnormal adiposity and laminitis), then a basal adrenocorticotrophic hormone (ACTH) test or dynamic testing, such as a thyrotropin-releasing hormone stimulation test, should be carried out (Durham and others 2014). It is still vital to evaluate insulin regulation in horses with PPID as insulin dysregulation is likely to be the common risk factor for laminitis and may explain why some horses with PPID get laminitis frequently and others do not (Morgan and others 2014a, Karikoski and others 2015).

## Assessment of insulin regulation

### Basal measurements

Haematology and serum biochemistry are rarely altered in EMS. Triglycerides may be mildly elevated in some cases and are correlated with serum insulin concentrations (Morgan and others 2014b). Basal glucose is rarely elevated due to the rarity of uncompensated insulin resistance, as previously discussed.

Basal insulin measurements are an important aid in the diagnosis of EMS, while also offering valuable information for monitoring progress, assessing laminitic risk and guiding interventions. While it is possible to detect insulin resistance in horses by demonstrating basal hyperinsulinaemia, false negatives may occur. In our experience, false positives are less common than false negatives. Basal insulin concentrations will be increased by feeding concentrates, although they are generally unaffected by low-medium, non-structural carbohydrate (NSC) roughage (eg, soaked hay or hay with low to moderate NSC) (Borgia and others 2011). Physiological stress in the form of acute exercise or pain will generally decrease insulin concentrations in horses, most likely attributable to increases in circulating catecholamines that inhibit insulin (Gordon and others 2007). Contrary to popular belief, there is no evidence to suggest that pain (eg, associated with laminitis) increases basal insulin. Pain in people does reduce glucose uptake, but does not affect basal insulin concentrations (Greisen and others 2001). Pain and illness, however, will increase basal ACTH concentrations (Towns and others 2010), and potentially affect a diagnosis of PPID.

The original cut-off values for insulin and laminitis risk of over 20  $\mu\text{IU/ml}$  were derived from pastured ponies held in yards for one to three hours before testing (Treiber and others 2006, Carter and others 2009). Despite this, it has been recommended that the basal insulin be measured following approximately six hours of fasting (Frank and others 2010). The authors suggest prolonged fasting is unnecessary and that horses should be sampled in the morning before any supplementary feeding and having been allowed access to preferably low NSC or soaked hay (rather than grazing) overnight. It is vital that the preparations undertaken before testing remain the same if tests are repeated.

For the purposes of determining serum insulin concentrations, the majority of UK laboratories use immunoassay techniques. The most commonly used is the Immulite 2000, which has been compared with the radioimmunoassay (Coat-a-Count; Siemens) and showed a good correlation, especially around the levels of diagnostic significance (A. E. Durham, personal communication, H. B. Carslake and others, unpublished data). If other assays are used, reference intervals may be different from the literature and need to be validated.

Proxies (insulin-sensitivity indices) calculated from insulin and glucose measurements estimate insulin sensitivity and pancreatic response (Muniyappa and others 2008). The two most common proxies used are: RISQI, the reciprocal of the square root of insulin, a measure of insulin sensitivity; and MIRC, the modified insulin ratio to glucose representing the ability of the pancreas to secrete insulin. Given these proxies are generated from basal measurements they are subject to similar limitations. However, as proxies convert non-linear values to linear values they may be more useful for monitoring over time than raw values.

If basal hyperinsulinaemia is not present and yet the phenotype of the horses strongly suggests EMS then dynamic testing should be undertaken.

### Dynamic testing

Dynamic testing gives a more complete picture of the insulin-glucose dynamics and, although the ideal test has not yet been determined, dynamic tests are more sensitive than basal tests (Frank and others 2010). Several intravenous tests that can be performed in the field have been developed, including the intravenous insulin response test (Bertin and Sojka-Kritchevsky 2013) and the combined glucose-insulin tolerance test (CGIT) (Eiler and others 2005).

The CGIT (Fig 2) is currently the recommended test for insulin sensitivity in clinical cases (Frank and others 2010), and has also been used in recent research studies on EMS (McGowan and others 2013, Morgan and others 2015). Measured insulin concentrations

have been shown to be more repeatable than glucose concentrations (Bröjer and others 2013), and thus may be preferred for follow-up of cases.

Other intravenous techniques, such as minimal model analysis, require frequent sampling following intravenous glucose and insulin, and computer modelling is used to generate measures of insulin sensitivity (Kronfeld and others 2005). This type of testing has been shown to have good correlation with clamping techniques, but is generally confined to the research setting.

Unlike intravenous dynamic testing, the oral glucose test (OGT) or oral sugar test (OST) determine the postprandial insulin response

and include the response of gastrointestinally derived hormones (the enteroinsular axis), rather than whole-body insulin sensitivity or resistance. Glucose/dextrose is administered at 0.5 to 1 g/kg with a small feed, and insulin is measured two hours postprandially (OGT) (Liphook Veterinary Laboratory, personal communication), or 150 mg/kg corn syrup may be administered directly into the mouth via a syringe and a blood sample collected for insulin 60 to 90 minutes later (OST) (Schuver and others 2014). Insulin over 85  $\mu$ iu/ml (OGT) or over 60  $\mu$ iu/ml (OST) would be considered diagnostic of EMS (Liphook Veterinary Laboratory, personal communication). The OST compares favourably to the intravenous glucose tolerance test,

but has not been evaluated against the CGIT (Schuver and others 2014). There are definite advantages to these tests in terms of the simplicity of the test, conducive to field use, but they have yet to be fully validated.

### Referral/specialist evaluation

Referral can play an important role in the diagnosis and management of difficult or equivocal cases of EMS or endocrinopathic laminitis. A referral centre may be able to carry out dynamic testing more easily and help in diagnosis of more complicated or equivocal cases. Additional blood parameters, such as triglycerides, leptin and IL-6 may be helpful in equivocal cases and may well become more commonplace as our understanding of the disease improves (Pleasant and others 2013, Basinska and others 2015).

### Treatment of EMS

Management of EMS in horses is based on a programme of dietary modifications and exercise. Reducing caloric intake and increasing energy expenditure are the mainstays for reducing obesity and improving insulin sensitivity. The primary goal is improvement in insulin sensitivity, measured as a reduction in basal hyperinsulinaemia and insulin response to oral or intravenous glucose challenge. Research has shown weight reduction in horses results in improved insulin sensitivity (Unguru and others 2013, Morgan and others 2015). Veterinary involvement is a key element in achieving owner compliance and significant weight loss, with good owner compliance improvements in CGIT results being seen within six to eight weeks (Morgan and others 2015).

### Diet

Dietary modification is the key to inducing weight loss in the majority of horses with EMS. It is essential to obtain a detailed history from the owner regarding the current feeding regimen and management of the horse, including options for grazing, exercise and confinement. Tailoring the diet to the individual needs of the horse leads to, very importantly, improved owner compliance and results in a better response to treatment (Morgan and others 2015).

The first step is to remove any concentrate feed from the diet, as well as any

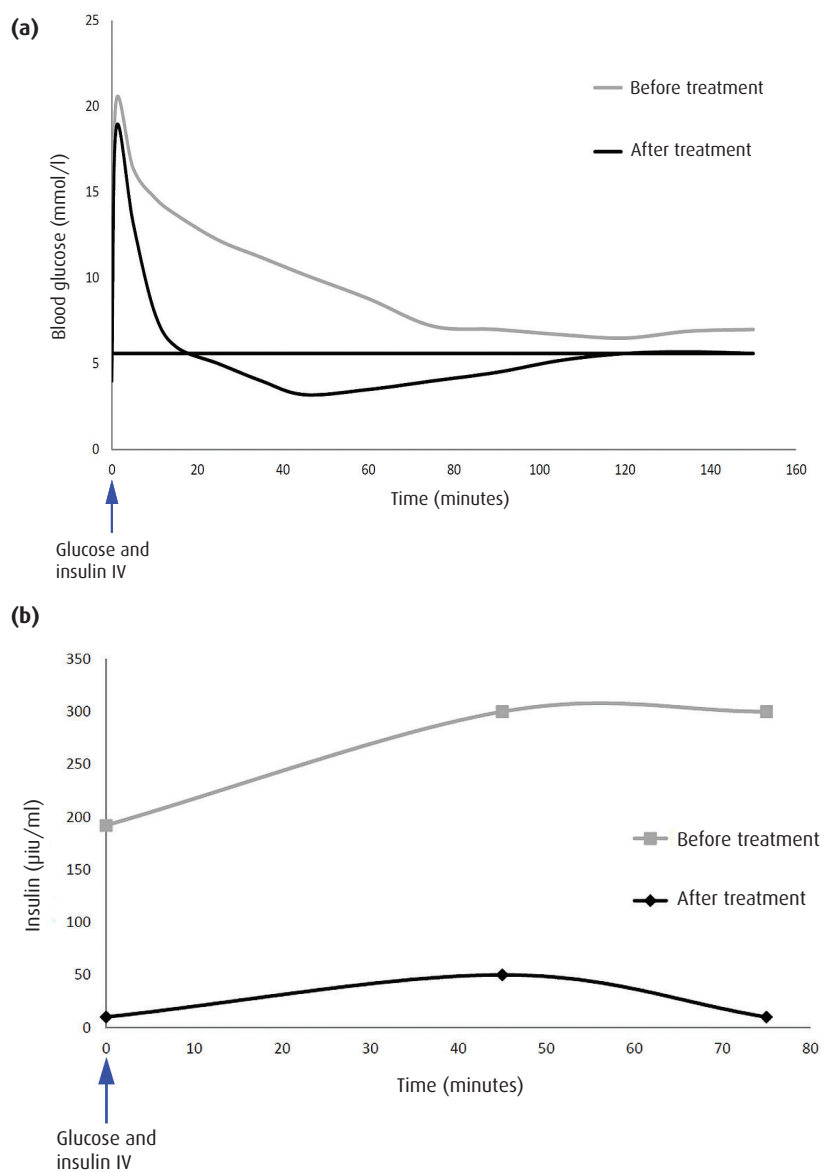


FIG 2: (a) Glucose and (b) insulin response to the combined glucose-insulin test in a pony before and after successful weight loss due to dietary management. The night before testing, house the horse in an accustomed environment, pre-place the catheter, feed low non-structural carbohydrate roughage overnight. Next morning, administer 150 mg/kg glucose (eg, for a 500 kg horse, 150 ml of 500 mg/ml [50 per cent] glucose, or 187.5 ml of 400 mg/ml [40 per cent] glucose), immediately followed by 0.10 units/kg of regular insulin (eg, 0.5 ml/500 kg horse of 100 iu/ml insulin [Humulin S; Eli-Lilly]). Blood samples for glucose should be collected before administration of glucose and tested immediately using a handheld glucometer validated for use in the horse (eg, Alphatrak), and then at one, five, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135 and 150 minutes (Eiler and others 2005, Frank and others 2010). Blood samples (plain tube) for insulin should be taken before glucose administration at 45 and 75 minutes. The interpretation from these tests: Blood glucose concentration should return to baseline within 45 minutes and insulin should be less than 100  $\mu$ iu/ml at 45 minutes and back to baseline by 75 minutes (Eiler and others 2005, Frank and others 2010). The test can be shortened for field use, with samples taken at 45 and 75 minutes only. Note that very insulin-sensitive animals may become hypoglycaemic at around 45 minutes. If weakness or muscle tremors are observed, offer the animal a small palatable feed

high sugar treats, such as apples. The diet should be forage based, with the aim of feeding low- to medium-NSC forage with less than 10 per cent NSC content (Frank and others 2010). NSC refers to carbohydrates usually found within the seeds and leaves of plants, and includes starches and simple sugars. Horses normally eat approximately 2 to 2.5 per cent (NRC 2007) and ponies up to 5 per cent (Argo and others 2012) of their bodyweight as dry matter (DM) in a 24-hour period when given ad lib access to food. It is recommended that to induce weight loss, the horse is fed approximately 1.25 per cent of their bodyweight in DM (approximately 1.5 per cent in fresh weight for hay of 80 to 85 per cent DM) per 24-hour period. Diets of less than 1 per cent of bodyweight DM are not recommended because of potential problems with hind gut function, hyperlipaemia, protein restriction and stereotypies (McGregor-Argo 2009).

Ideally, the NSC content of the available forage should be determined to inform recommendations and several feed companies offer this service commercially. In the absence of this information, soaking is a simple, and frequently recommended, method of reducing the NSC content of hay. Soaking hay in cold water for 60 minutes reduces the water soluble sugar content by approximately 30 per cent (Watts and Chatterton 2004), although soaking for eight to 16 hours has been shown to result in reduction of water soluble sugars of up to 50 per cent (Longland and others 2011, Mack and others 2014). Soaking also results in a loss of water soluble macrominerals (potassium, sodium, magnesium, calcium and phosphorus), which will need to be supplemented (Martinson and others 2012, Mack and others 2014). Hay soaking can also result in losses of up to 25 per cent DM (Argo and others 2015), so soaking hay should only be recommended with higher volumes of feed fed (2 per cent of current bodyweight fresh weight or greater), or under strict veterinary guidance. Soaking haylage is not recommended, due to the risks of increased bacterial fermentation. A commercial high-quality balancer should be given to provide adequate total daily requirements of vitamins and minerals. Low calorie balancers often have relatively greater protein restriction than caloric restriction and are not recommended.

Chaff-based, low-NSC feeds, which are designed to provide low NSC and are combined with a complete balancer, are an option in horses that do not like soaked hay or for owner convenience, but these can be expensive (Dugdale and others 2011).

Achieving weight loss in horses and ponies kept at pasture can be difficult and unrewarding as it is impossible to determine caloric intake. Often, it is preferable to confine the animal in a stable at the start to aid initial weight loss. Many horses and ponies can be returned to restricted grazing by using bare fields, sand maneges or by use of a grazing muzzle, following improvement or normalisation of their CGIT results (Morgan and others 2015). It is important, however, to counsel owners about how to fit and manage a grazing muzzle. Strip grazing or short periods of access to grass can be counterproductive, as ponies that have restricted grazing have been found to rapidly compensate and can ingest almost 50 per cent of their daily DM intake for 24 hours in just three hours of grazing (Ince and others 2011).

## Exercise

Exercise not only induces weight loss but also independently improves insulin sensitivity in people and animals. Ponies exercised on a treadmill for six weeks showed improvement in insulin sensitivity, which was maintained even after six weeks of deconditioning (Freestone and others 1992). Dietary restriction combined with exercise was shown to improve insulin sensitivity in obese insulin resistant ponies (Ungru and others 2013), although light exercise without dietary restriction may not be sufficient (Carter and others 2010).

Exercise is necessarily limited in horses with EMS if they have acute or chronic active laminitis, and could be very detrimental in an unstable case. Ideally, however, as soon as the horse is comfortable off all analgesic/anti-inflammatory medication and has appropriate solar support, exercise may begin. The exercise should be tailored to the individual animal, taking into account their breed, level of fitness and the facilities available to the owner. Starting with short periods of exercise on a soft surface, such as a manege, may be ben-

eficial. There is limited evidence as to the best protocol, but exercise should progress up to 15 minutes of trotting exercise per day to maximise glycogen use (Hodgson and others 1985). The horse should be monitored closely for a flare-up of laminitis or increased pain. Even though pasture turnout may be insufficient to improve insulin sensitivity (Turner and others 2011), removal of exercise by confinement can be a trigger factor for laminitis in EMS horses (Wylie and others 2013). Therefore, any reductions in exercise should be managed carefully by concurrent caloric restriction in EMS horses.

## Pharmacological interventions

Metformin is an anti-hyperglycaemic drug used predominantly within a dual therapy regimen for treatment of type 2 diabetes or prediabetes in people, in whom it is thought to suppress hepatic glucose production and indirectly stimulate AMP-activated protein kinase, a major regulator of cellular and whole-body energy homeostasis. It also appears to have other secondary effects, including reducing absorption of glucose from the gut, improving blood glucose homeostasis, lipid profile and blood pressure. Previous studies showed an improvement in basal measures of insulin sensitivity in a small number of insulin resistant horses when the drug was administered at a dose of 15 mg/kg (Durham and others 2008, Durham 2011). However, the oral bioavailability of metformin in horses is reported as only 7.1 per cent in unfed horses and 3.9 per cent in fed horses (Hustace and others 2009), and more recent research has shown a lack of efficacy of the drug on insulin sensitivity in both normal and insulin resistant horses (Tinworth and others 2010a, 2012). Recent work indicated some reduction in glucose absorption from the small intestine in experimental horses treated with metformin (Rendle and others 2013), a finding that warrants further investigation. While this may indicate a role for metformin in the early stages of laminitis, management to reduce carbohydrate absorption, the recommended low-soluble carbohydrate diet of such cases, possibly precludes any perceived benefit from longer-term drug administration.

Research by Frank and others (2005, 2008a, b) found that euthyroid horses that were administered levothyroxine had significant weight loss and improvement in insulin sensitivity over eight- and 48-week periods, with no cardiovascular side effects. These studies did not, however, control the diet of the horses treated and, as such, further work is required to determine an accurate efficacy of levothyroxine. It is our recommendation that horses treated with levothyroxine should not be confined to a stable, due to the potential welfare aspects of confinement when administered an activity-inducing drug.

Thiazolidinediones, such as pioglitazone and rosiglitazone, are insulin-sensitising drugs used to treat type 2 diabetes in people. There is very little evidence to support the use of these drugs in horses; a recent study using lipopolysaccharide to induce insulin resistance in healthy horses showed that pioglitazone failed to improve insulin sensitivity or mitigate the effects of lipopolysaccharide on insulin sensitivity (Suagee and others 2011).

The use of nutraceuticals and supplements in EMS has received some attention in recent years based on their perceived importance in people in management of metabolic syndrome (Tinworth and others 2010b). Dietary supplementation with short-chain fructooligosaccharides (ScFOS) has been shown to increase insulin sensitivity in obese horses without dietary restriction (Respondek and others 2011), but no additional insulin-sensitising effects of the nutraceutical were seen when dietary restriction was used in combination with ScFOS in a randomised crossover trial (McGowan and others 2013). The mechanism of action is unclear, but is likely related to enhanced bacterial fermentation in the stomach and colon (Respondek and others 2007); further work is required to improve our understanding. Chromium has been suggested to improve insulin sensitivity by altering the intracellular signalling pathways initiated by the activated insulin receptor (Hummel and others 2007). However, chromium had no effect on weight or insulin sensitivity in horses when fed for 16 weeks (Chameroy and others 2011). Similarly, disappointing results were demonstrated in horses given cinnamon or omega-3 fatty acids twice daily for 10 days (Earl and



others 2012). L-carnitine was shown to improve glucose tolerance in one study (Van Weyenberg and others 2009), but these results could not be replicated in further studies (Schmengler and others 2013).

## Conclusion

EMS is an important disease of horses and ponies characterised by obesity, insulin resistance and a predisposition to laminitis. Our understanding of the underlying mechanisms of the disease is still limited, but it is an area of active research. Diagnosis of EMS is reliant on demonstrating insulin resistance using basal or dynamic testing, as well as recognition of the risk factors, such as obesity and breed predisposition. Early identification of at-risk animals using tests for basal and dynamic insulin regulation may help to prevent the development of laminitis if appropriate management is employed. The mainstay for treatment of EMS is weight reduction, with a combination of dietary modification and exercise in horses without painful or unstable laminitis.

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