

# Current Understanding of Equine Metabolic Syndrome

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Based on current evidence, elevated triglyceride concentrations and disturbances in insulin dynamics (fasting hyperinsulinemia and/or exaggerated insulin response to oral or intravenous glucose administration) are the most consistent features of the equine metabolic syndrome (EMS) phenotype. Whereas obesity and/or regional adiposity have been widely regarded as a primary feature of EMS, our recent findings suggest that obesity per se may not be a primary driver of the syndrome. Instead, obesity may be a marker of an underlying metabolic dysfunction that, depending on other environmental factors (eg, diet, level of physical activity), drives adipose tissue accretion and development of obesity. Thus, the presence or absence of obesity should not be used as a diagnostic criterion. Furthermore, although dietary restriction for correction of obesity remains an important management goal, the underlying metabolic dysfunction in affected animals may persist after weight loss. It is evident that further research is needed to better elucidate the EMS phenotype as well as its underlying pathophysiology. It is possible—even likely—that the syndrome that we now term EMS actually represents more than one condition. Thus, as new information becomes available, a change in the definition of EMS, even the name itself, may be warranted. Authors' addresses: Department of Large Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University, 736 Wilson Road, East Lansing, MI 48824 (Geor); Department of Veterinary Population Medicine, College of Veterinary Medicine, University of Minnesota, 1365 Gortner Avenue, St Paul, MN, 55108 (McCue, Schultz); e-mail: geor@cvm.msu.edu. \*Corresponding and presenting author. © 2013 AAEP.

## 1. Introduction

Equine metabolic syndrome (EMS) refers to a cluster of clinical abnormalities associated with an increased risk of laminitis.<sup>1,2</sup> Although reports describing a phenotype that we now recognize as EMS were published as far back as the 1970s,<sup>3</sup> the term EMS was not introduced to the equine medicine vernacular until the early part of the last decade.<sup>1</sup> A number of different names have been used to

describe this condition, including obesity-associated laminitis, peripheral Cushing's syndrome, and pre-laminitic metabolic syndrome. The terms endocrinopathic laminitis and pasture-associated laminitis add to the confusion over nomenclature. Endocrinopathic laminitis refers to laminitis arising from hormonal rather than inflammatory conditions; by this definition, EMS-associated laminitis (and the laminitis that occurs in association with

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## NOTES

**Table 1. Summary of Findings Related to Obesity, Regional Adiposity, and Endocrine/Metabolic Variables in Published Studies of the Equine Metabolic Syndrome Phenotype**

	Treiber et al, 2006 <sup>5*</sup>	Frank et al, 2006 <sup>8</sup>	Bailey et al, 2008 <sup>6</sup>	Carter et al, 2009 <sup>7*</sup>
Breed(s)	Welsh/Dartmoor ponies	Six breeds	Mixed-breed ponies	Welsh/Dartmoor ponies
Sample size	160	12	80	74
Obesity (BCS) in EMS	Yes	Yes	No	Yes
Regional adiposity in EMS	Yes	Yes	No	Yes
Hyperinsulinemia in EMS	Yes (21.6 vs 10.7 mU/L)	Yes (50.5 vs 9.1 mU/L)	Yes† (69.5 vs 21.5 mU/L)	Yes (20.5 vs 8.8 mU/L)
Insulin resistance in EMS	Yes (RISQI)	Yes (CGIT)	Yes† (RISQI)	Yes (RISQI)
Fasting glucose	Not different	Higher in EMS (83.9 vs 66.9 mg/dL)	Not different	Not different
Triglycerides	Higher in EMS (97.2 vs 52.3 mg/dL)	Not different	Higher in EMS† (0.55 vs 0.38 mmol/L [49.0 vs 34.0 mg/dL])	Higher in EMS (53.0 vs 39.0 mg/dL)
NEFAs	Not different	Higher in EMS (366.5 vs 197.1 $\mu$ mol/L)	Not evaluated	Not evaluated

BCS indicates body condition score; RISQI, reciprocal of the square root of the serum insulin concentration; CGIT, combined glucose-insulin tolerance test; NEFAs, nonesterified fatty acids.

\*Data obtained from the same population of Welsh and Dartmoor ponies.

†Serum insulin and triglyceride concentrations and RISQI differed between ponies with and without a history of laminitis in summer but not in winter.

pituitary pars intermedia dysfunction) can be regarded as endocrinopathic in origin. Similarly, pasture-associated laminitis has sometimes been used synonymously with EMS. This report describes current understanding of the clinical features of EMS as well as underlying pathophysiology. Other papers in this *In-Depth* series describe methods for diagnosis of EMS and aspects of nutritional and medical management.

## 2. Defining the EMS Phenotype

Johnson<sup>1</sup> recognized that primary features of a laminitis-prone phenotype (ie, obesity, insulin resistance) were analogous to those described for the metabolic syndrome (MetS) in humans, which is a constellation of abnormalities, including obesity, dyslipidemia, glucose intolerance, and hypertension associated with increased risk of cardiovascular disease and perhaps also diabetes mellitus.<sup>4</sup> The suggestion that the underlying pathophysiology of EMS is similar to that of MetS and the increased clinical recognition of “EMS” has spurred a number of observational and experimental studies in the past decade. Data emerging from these studies have provided some insight regarding features of the phenotype and its pathophysiology.

In a published consensus statement from the American College of Veterinary Internal Medicine (ACVIM),<sup>2</sup> the EMS phenotype was defined by the following criteria.

- (1) Generalized obesity and/or increased adiposity in specific locations (regional adiposity): An increase in the amount of fat

surrounding the nuchal ligament (“cresty neck”) is a common example of regional adiposity in affected animals but abnormal fat deposits also may be evident close to the tail head, behind the shoulder, or in the prepuce of the mammary gland region.

- (2) Insulin resistance (IR) characterized by hyperinsulinemia and/or abnormal glycemic and insulinemic responses to oral or intravenous (IV) glucose or insulin challenges.

- (3) A predisposition toward laminitis that develops in the absence of other recognized causes, such as grain overload, retained placenta, colitis, colic, or pleuropneumonia.

However, descriptions of the metabolic phenotype of laminitis-prone horses and ponies have varied among published studies (Table 1),<sup>5–8</sup> and the features that define EMS are a subject of ongoing debate in the equine veterinary community. What has become increasingly clear is that the relationships between the primary phenotypic features and key diagnostic measurements in EMS are complex—its phenotypic manifestation is highly influenced by environment; variation in measurements between individuals caused by breed, age, sex, and other factors make it difficult to establish clear diagnostic criteria; and not all components of the syndrome (eg, obesity) may be present in individuals with underlying metabolic derangements. In the following sections, we discuss these key criteria, the current scientific data that support/refute these criteria, and what is known regarding the pathophysiology of EMS.

### 3. IR and Hyperinsulinemia

Although our understanding of the etiology and pathophysiology of EMS is far from complete, it seems likely that IR and/or hyperinsulinemia play an important role. From a biological viewpoint, IR is usually defined in terms of the reduced ability of a given concentration of insulin to lower blood glucose levels. There has been much discussion about IR in the context of EMS; however, very few studies have reported quantitative data on insulin sensitivity and other aspects of glucose and insulin dynamics in affected animals.<sup>8–10</sup> Furthermore, the clinical definition and recognition of IR in equine medicine are not straightforward because “gold standard” methods for assessment of insulin sensitivity cannot be readily applied in clinical practice while simpler methods are either highly labile (eg, measurement of fasting insulin and glucose concentrations) or have not been thoroughly evaluated as valid surrogate indicators of insulin sensitivity (eg, fasting insulin; combined glucose-insulin tolerance test). The recognition of significant breed differences in insulin sensitivity, fasting insulin concentrations, and insulin responses during an oral sugar test (OST) further complicates development of a universal clinical definition of IR in horses.

The majority of reports have used “fasting” or “resting” measures of insulin and glucose and/or indices derived from these measurements (eg, the reciprocal of the square root of insulin concentration) as surrogate indicators of IR. Hyperinsulinemia has been shown to be a feature in the EMS phenotype in ponies<sup>5–7</sup> and Morgan horses,<sup>8</sup> although there is wide variation in values among studies that may in part be explained by differences in sampling conditions (eg, feed withholding versus pasture grazing before collection of blood samples). The current consensus view is that a fasting insulin concentration >20 mIU/L indicates IR. In a sample of 300 healthy, nonlaminitic horses in southwest Virginia, the prevalence of basal hyperinsulinemia (defined as insulin concentration >20 mIU/L) was 18%,<sup>11</sup> whereas another study in Australia reported a 28% prevalence of hyperinsulinemia (same cutoff value) in randomly selected ponies.<sup>12</sup> In the pony study, age, body condition score (BCS), supplementary feeding, and a history of laminitis were identified as risk factors for hyperinsulinemia.<sup>12</sup>

Fasting hyperinsulinemia is typically (but not always) accompanied by normoglycemia, which suggests compensated IR, that is, an increase in pancreatic insulin secretion occurs in response to reduced tissue insulin sensitivity, resulting in maintenance of glucose homeostasis. Two studies in ponies that used minimal model analysis of a frequently sampled glucose tolerance test have provided evidence of compensated IR, indicated by lower insulin sensitivity, higher acute insulin response to glucose administration (a measure of insulin secretion), and no difference in glucose tol-

erance when comparing laminitis-prone to nonlaminitic ponies.<sup>9,10</sup> In the early stages of type 2 diabetes of humans, hyperinsulinemia is also considered to be a compensatory response to IR. However, there also are some data suggesting that hyperinsulinemia per se can induce IR.<sup>13</sup> Thus, it may be questioned whether hyperinsulinemia in EMS is the “cart or the horse.”

Mechanisms other than a compensatory increase in pancreatic secretion to counter tissue insensitivity may contribute to the fasting hyperinsulinemia and exaggerated insulinemic response to glucose administration observed in EMS animals. The plasma or serum concentration of insulin is primarily determined by its rate of secretion and clearance, with approximately 80% of endogenous insulin removed by the liver.<sup>14</sup> In humans and some animal species, there is evidence of decreased insulin clearance in insulin-resistant states (eg, diabetes mellitus, obesity, nonalcoholic fatty liver disease).<sup>15,16</sup> This reduction in insulin clearance is thought to be a mechanism to preserve  $\beta$ -cell function and also to maintain peripheral insulin levels in the face of IR.<sup>16</sup> One recent study in horses has shown that reduced insulin clearance contributes to higher blood insulin concentrations in obesity,<sup>17</sup> and it is also possible that decreased insulin clearance is a factor in the hyperinsulinemia observed in EMS animals.

Other hormones may contribute to an “upregulation” of insulin secretion in EMS, for example, the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which are secreted by the gut in response to nutrient cues. GLP-1 and GIP are labeled incretin hormones because they potentiate glucose-mediated insulin secretion and account for the higher insulin secretory response that is elicited by oral when compared with IV administration of glucose.<sup>18</sup> The insulinotropic action of GLP-1 was augmented in high-fat-fed obese and insulin-resistant mice compared with normal mice.<sup>19</sup> Studies in humans have yielded conflicting information regarding the effects of obesity and type 2 diabetes on incretin hormone secretion and the incretin effect.<sup>20,21</sup> One view, however, is that these conditions result in impairment in secretion and/or action of incretin hormones, and current studies are focused on the potential benefits of incretin-based therapy in type 2 diabetes.<sup>20</sup> At present, there is no published information on incretin hormone secretion or action in EMS.

There may be breed and/or genetic variation in insulin sensitivity and dynamics that affects susceptibility to EMS. Several review articles have raised the possibility of breed predisposition to EMS, with Welsh and Dartmoor ponies, Morgans, Tennessee Walking Horses (TWH), Saddlebreds, Arabian, and Paso Fino breeds thought to be more susceptible.<sup>1,2,22</sup> Affected horses and ponies appear to have high metabolic efficiency, meaning

that they require fewer calories for maintenance of body weight when compared with unaffected animals (ie, they are “easy keepers”). Ponies in general have lower insulin sensitivity<sup>23</sup> and a higher prevalence of hyperinsulinemia when compared with horses.<sup>11,12</sup> Given the observational<sup>5–8</sup> and experimental evidence<sup>24,25</sup> linking hyperinsulinemia to laminitis, it is possible that these inherent differences in insulin sensitivity and dynamics contribute to the higher clinical expression of EMS in ponies. Ponies also tend to consume more feed than horses when provided ad libitum access, which may contribute to exacerbation of hyperinsulinemia and risk of laminitis especially in animals maintained at pasture.

In human MetS, IR and/or hyperinsulinemia are thought to contribute to other components of the syndrome including dyslipidemia and vascular endothelial dysfunction that can lead to persistent hypertension.<sup>26</sup> Increased de novo hepatic lipogenesis is a feature of IR and hyperinsulinemia in humans and in animal models.<sup>27</sup> Activation of the mammalian target of rapamycin complex-1 and subsequent induction of sterol regulatory element-binding protein-1c, a master regulator of hepatic lipogenesis, is one possible mechanism for hyperlipidemia and increased hepatic fat accumulation in insulin-resistant states.<sup>28</sup> Increased plasma triglyceride concentrations were a feature of the EMS phenotype in a closed herd of Welsh ponies<sup>5</sup> and in outbred ponies with a history of recurrent laminitis,<sup>6</sup> although in the latter study the relative hypertriglyceridemia was evident during summer but not winter. An increase in nonesterified fatty acid (NEFA) delivery to the liver may be an alternative or additional factor underlying increased lipid concentrations.<sup>29</sup> In a small, mixed-breed group of obese, insulin-resistant horses, increased serum NEFA concentrations (but not triglycerides) were detected,<sup>8</sup> whereas serum NEFAs were not useful in the differentiation of an EMS phenotype in ponies,<sup>5,7</sup> and increased serum NEFA has not been a feature of the EMS phenotype in our recent study of >600 horses (below). In one report, increased very-low-density lipoprotein triglyceride concentrations were observed in horses with EMS.<sup>8</sup>

Insulin contributes to the regulation of vascular tone through effects on the synthesis and release of nitric oxide (NO; a vasodilator) and endothelin-1 (ET-1; a vasoconstrictor).<sup>30</sup> In other species, NO synthesis is impaired in IR, whereas hyperinsulinemia itself stimulates increased ET-1 production; the resultant imbalance between NO and ET-1 favors vasoconstriction and is thought to contribute to hypertension in insulin-resistant states such as MetS and type 2 diabetes mellitus.<sup>31</sup> Bailey et al<sup>6</sup> detected arterial hypertension in mixed-breed, recurrent laminitic ponies during summer but not in winter, whereas in our own studies, mean blood pressure did not differ between groups of EMS versus non-EMS ponies when measured in early spring,

summer, and fall.<sup>32</sup> Further research is therefore needed to determine whether or not vascular endothelial dysfunction is a feature of EMS.

#### 4. Obesity

Similar to the situation in human populations, the prevalence of obesity in horse and pony populations appears to be on the rise, and there is a growing concern regarding the adverse health effects of an expanded fat mass.<sup>33</sup> One definition of obesity in horses is a BCS  $\geq 7/9$  (Henneke scale), with recent studies showing that body fat represents ~20% to 25% of total mass in the animals with a BCS at or above this cutoff.<sup>34,35</sup> The prevalence of obesity in horse and pony populations, defined as a BCS  $\geq 7/9$ , has varied between ~20% and ~50% in recent studies,<sup>36,37</sup> whereas obesity has been proposed as a risk factor for pasture-associated laminitis in ponies.<sup>5,7</sup> Certainly, obesity and/or the presence of one or more enlarged subcutaneous fat deposits (regional adiposity) have been regarded as defining characteristics of EMS.<sup>2,22</sup> Anecdotally, horses and ponies diagnosed with EMS may be obese and/or have regional fat accumulation in the nuchal ligament region (cresty neck), behind the shoulder (unilateral or bilateral), around the tail-head, and in the preputial or mammary gland regions. Occasionally, the presence of abnormal swelling around the prepuce or mammary glands caused by adipose tissue deposits and associated edema is the presenting complaint.<sup>22</sup> In published studies, high BCS and measures of apparent neck crest fat accumulation (“cresty neck score,”; neck circumference-to-height ratio, NCHR) have been associated with the EMS phenotype in horses and ponies<sup>5,7,8</sup>; however, obesity has not been a consistent finding across studies.<sup>6</sup> Additionally, definitions of obesity have varied among studies (eg, BCS  $>6/9$ <sup>5</sup> versus BCS  $>7/9$ <sup>8</sup>; Henneke scale).

Information from a recent study of >600 horses and ponies with (PL) and without (NL) a history of laminitis (previous 12 months) has provided further insight into the EMS phenotype, including the association with obesity.<sup>38</sup> The data collected included morphometric measurements and indices (eg, BCS, NCHR, girth-to-height ratio), fasting glucose, insulin, triglyceride and leptin concentrations, and glucose and insulin concentrations 75 min after an oral sugar challenge (OST; 15 ml corn syrup per 100 kg BW). The predominant breeds sampled were Morgan horses, TWH, Arabians, and Welsh ponies. Across breeds, fasting insulin concentration, insulin 75 minutes after corn syrup administration, and fasting serum triglycerides were the variables most consistently elevated in animals with a history of laminitis. This observation confirms previous results in ponies<sup>5,6</sup> but, in contrast to another report,<sup>8</sup> demonstrates that elevated serum triglycerides might also be a key feature of the EMS phenotype in horses. Unlike some previous reports, morphometric measures (NCHR, etc) and BCS did not discriminate between the PL and NL groups. Prior weight

loss in PL animals may have confounded this assessment, although it is noteworthy that within the PL cohort metabolic variables (insulin, triglycerides, etc) did not differ between obese (BCS  $\geq 7$ ) and non-obese (BCS  $< 7$ ) animals, suggesting that the metabolic derangement persists even after weight loss. Within the NL cohort, however, serum triglycerides, fasting insulin, and post-OST insulin were higher in obese when compared with nonobese animals. One interpretation of these findings is that obesity per se is not a requisite feature of the laminitis-prone (ie, EMS) phenotype, but components of the phenotype such as IR may be exacerbated when affected animals become obese.<sup>38</sup> This interpretation is consistent with anecdotal clinical observations of the laminitis-prone phenotype—not all affected animals express obesity or regional adiposity, whereas, conversely, not all obese animals appear to be at increased risk of laminitis. Simply put, obesity in and of itself does not equate with EMS.

In humans, too, it is now recognized that the presence of obesity-related metabolic disturbances, including IR, hyperlipidemia, inflammation, and hypertension, varies widely among obese individuals.<sup>39,40</sup> In fact, in some studies, up to 30% to 35% of obese adult humans have a metabolically healthy phenotype, giving rise to the term “metabolically healthy obese.”<sup>39</sup> On the other hand, up to 40% of adults of normal weight and body mass index have metabolic perturbations typically associated with obesity and MetS, such as dyslipidemia, hyperinsulinemia, and nonalcoholic fatty liver disease.<sup>39,40</sup> Although the mechanisms underlying these different phenotypes are not fully understood, it is currently believed that differences in visceral fat accumulation and the response of adipocytes to increased lipid accumulation are important factors.<sup>39</sup> Adipose tissue produces a large array of proteins, including pro-inflammatory cytokines and other hormone-like proteins termed adipokines that exert local (paracrine) and systemic (endocrine) effects.<sup>41</sup> Studies in animal models have indicated that obesity results in a progressive dysregulation of adipose tissue function, including marked pro-inflammatory signaling that leads to the development of a systemic inflammatory response, which, in turn, results in the development of IR and other metabolic abnormalities.<sup>41,42</sup> However, not all excess fat carries equal risk with visceral adiposity most strongly associated with systemic inflammation and IR, perhaps because of higher cytokine and adipokine production as well as release of NEFAs into the portal circulation that contribute to the development of hepatic IR.<sup>42</sup>

Our preliminary observations that obesity per se is not a defining feature of EMS mirrors findings in humans—IR and hypertriglyceridemia can occur in nonobese horses, whereas, conversely, the metabolic profile of some obese horses does not differ from that in lean individuals. One hypothesis is that obesity is not a primary cause of EMS but instead it may be

a marker of an underlying metabolic dysfunction, which, depending on other environmental factors (eg, diet, level of physical activity), drives adipose tissue accretion and development of obesity. If so, there are two very important implications for the identification and management of EMS. First, the presence or absence of obesity cannot be used as a diagnostic criterion. Second, whereas dietary restriction and weight loss may result in some improvement in insulin sensitivity and so forth in affected animals, the underlying metabolic dysfunction is likely to persist. Thus, a diagnosis of EMS may be justified in some horses and ponies with recurrent laminitis problems that are not obese (or show regional adiposity) because they have other components of the phenotype, for example, hyperinsulinemia or high serum triglycerides. Then again, a diagnosis of EMS is not appropriate in horses or ponies that are obese (BCS  $\geq 7$ ) but without evidence of laminitis or disturbances in insulin dynamics and lipid metabolism.

Further studies are needed to examine the impact of obesity on the metabolic health of horses and its role in EMS. Cross-sectional studies have shown an inverse relationship between BCS and insulin sensitivity<sup>43</sup> as well as positive relationships between apparent adiposity, resting insulin concentrations, and blood markers of inflammation (eg, serum amyloid A, tumor necrosis factor (TNF)- $\alpha$ , mRNA encoding for interleukin (IL)-1 $\beta$ , and TNF- $\alpha$ ).<sup>43,44</sup> On the other hand, adipose tissue (nuchal crest fat) and systemic markers of inflammation were unchanged in Arabian geldings after a 20% weight gain (increase in mean BCS [Henneke scale] from 6/9 to 8/9).<sup>a</sup> Additionally, insulin sensitivity was unchanged in Thoroughbred geldings after an  $\sim 15\%$  increase in body weight,<sup>45</sup> whereas another recent study of horses and ponies reported no change in insulin sensitivity after an  $\sim 20\%$  increase in fat mass.<sup>46</sup> These observations reinforce the idea that factors other than BCS and adipose tissue mass contribute to variance in insulin sensitivity.

Research is also needed to examine the role of the adipokines leptin and adiponectin in EMS. Leptin, the product of the *ob* gene, provides information to the brain regarding the availability of body fat stores, promoting satiety and a reduction in food intake when energy balance is positive or fat stores are plentiful.<sup>47</sup> Circulating leptin concentrations are generally in direct proportion to body adipose mass.<sup>41,47</sup> In contrast, serum adiponectin concentrations generally correlate inversely with fat mass, although in humans, hyperinsulinemia is associated with hypoadiponectinemia independent of fat mass.<sup>41</sup> It has been proposed that high leptin and low adiponectin concentrations are useful markers of IR and EMS.<sup>22</sup> Certainly, high leptin concentrations have been observed in insulin-resistant horses and ponies,<sup>7,8</sup> including nonobese animals. In our own studies, however, serum leptin was not useful for the identification of laminitis-

prone animals, although, consistent with previous studies, leptin concentrations were strongly associated with BCS. Similarly, an inverse relationship between blood adiponectin (total or high-molecular-weight forms) concentrations and BCS has been reported in horses.<sup>48,49</sup>

### 5. Laminitis

A current or recent episode of laminitis is the most common reason for a horse or pony to be evaluated for EMS.<sup>2,22</sup> The severity of EMS-associated laminitis is variable, ranging from subclinical (ie, the presence of divergent growth rings on the hoof wall but not overt lameness) to mild lameness that is only detected when horses move across a hard or uneven surface, to more severe lameness and other classical signs of laminitis. Laminitis tends to be recurrent in affected animals.<sup>22</sup> The results of informal surveys of practitioners support the impression that the majority of laminitis cases in practice are secondary to EMS,<sup>50</sup> and clinical observations suggest that EMS horses or ponies often develop laminitis when grazing at pasture (pasture-associated laminitis), especially under conditions that favor increased accumulation of water-soluble carbohydrates (WSC) in pasture forages, for example, spring and early summer, or after substantial rainfall in the summer or fall.<sup>5,51</sup> It has been suggested that EMS-associated laminitis begins as a seasonal problem, with episodes coincident with changes in pasture WSC content, but then becomes a year-round problem as the disease progresses.<sup>52,53</sup> In our own studies, incident laminitis in horses or ponies with suspected EMS was associated with pasture grazing in ~55% of cases.<sup>38</sup> EMS-associated laminitis, therefore, also appears to occur in circumstances not associated with exposure to pasture or other changes in diet composition. Another hypothesis is that animals with an EMS phenotype are more susceptible to sepsis-associated laminitis (ie, colitis, colic, Gram-negative sepsis), although data in support of this notion are lacking. There is an obvious need for data from well-designed epidemiological studies, such as the ongoing American Association of Equine Practitioners Foundation-supported case-control study of pasture- and endocrinopathy-associated laminitis, to determine the prevalence of EMS-associated laminitis and to provide evidence-based information on risk factors such as season, access to pasture, metabolic phenotype, and concurrent disease.

The discovery that prolonged hyperinsulinemia can induce laminitis in healthy horses and ponies may have important implications for understanding of EMS- and pasture-associated laminitis, providing a potential explanation for episodes of disease after consumption of feeds and forages that elicit pronounced insulinemic responses. Studies of grazing horses have shown a positive relationship between pasture NSC content and circulating insulin concentrations,<sup>54</sup> and marked exacerbation of hyperinsu-

linemia has been observed in ponies with an EMS phenotype when they are grazing spring pasture (NSC ~15–18% DM); moreover, the hyperinsulinemia coincided with episodes of laminitis in the EMS ponies.<sup>5,32</sup> Whether or not hyperinsulinemia plays an essential or exclusive role in the development of EMS-associated laminitis remains to be determined. Clinical observations have indicated that not all animals with profound and persistent hyperinsulinemia develop clinical laminitis, whereas, conversely, some animals with an EMS phenotype are not hyperinsulinemic during episodes of laminitis. Circulating insulin concentrations can vary markedly in EMS animals; therefore detection of an association between hyperinsulinemia and incident laminitis is challenging. Nevertheless, it also must be considered that other mechanisms may contribute to the development of laminitis in EMS.

The association between grazing NSC-rich pasture and incident laminitis in EMS animals raises the possibility of hindgut carbohydrate overload as a triggering mechanism. If a chronic inflammatory state is a component of EMS, then affected animals may be more susceptible to inflammatory injury of the lamellar tissues in the face of carbohydrate overload, which, in the experimental starch and oligofructose models,<sup>53</sup> elicits marked systemic and laminar inflammatory responses. In a recent study of insulin-resistant ponies, however, the feeding of a high NSC diet for 7 days that mimicked exposure to spring pasture had no effect on laminar pro-inflammatory signaling but did result in exacerbation of hyperinsulinemia.<sup>55</sup>

Vascular endothelial dysfunction caused by IR and/or hyperinsulinemia also may affect susceptibility to laminitis in EMS.<sup>53</sup> It is noteworthy that in healthy horses and ponies, an infusion of insulin that induces marked hyperinsulinemia (~1000 mU/L) causes an increase in hoof wall temperature that suggests digital vasodilation.<sup>25</sup> On the other hand, prolonged exposure of equine vascular tissue to high concentrations of insulin in vitro resulted in deterioration of vasodilatory responses.<sup>56</sup> More research is therefore needed to elucidate the interrelationships between IR, hyperinsulinemia, and digital hemodynamics in the context of laminitis susceptibility.

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