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Review Article

Equine Metabolic Syndrome: A Complex Disease Influenced by Genetics and the Environment

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ABSTRACT

Equine metabolic syndrome (EMS) refers to a cluster of clinical abnormalities including insulin resistance, generalized obesity, and/or increased adiposity in specific locations (regional adiposity) associated with an increased risk of laminitis. However, descriptions of the metabolic phenotype of laminitis-prone horses and ponies have varied among published studies. The metabolic phenotypes routinely measured (e.g., insulin, insulin responses, adipokines, adiposity, and so forth) are highly influenced by the environment and vary due to physiologic factors such as age, breed, and sex, even in normal individuals. Furthermore, not all components of the syndrome (e.g., obesity) may be present in individuals with underlying metabolic derangements. The complexity of the "EMS" phenotype has lead to an ongoing debate as to the canonical features that define the syndrome. Furthermore, little is understood about its pathophysiology. A better understanding of EMS requires a clearer phenotypic definition of EMS; a better grasp of the effects of both intrinsic and extrinsic factors that influence metabolic measures; and an appreciation of the complex interactions between the phenotypic components of the syndrome and the proposed risk factors. In this review, we will summarize the understanding of the EMS phenotype and propose a complex disease model that may help explain the variability in EMS.

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1. Introduction

Equine metabolic syndrome (EMS) refers to a cluster of clinical abnormalities associated with an increased risk of laminitis [1,2]. In 2002, Johnson [1] recognized that primary features of a laminitis-prone phenotype (i.e., 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 type 2 diabetes mellitus [3–5]. Work by a number of authors has documented similarities between EMS and MetS (Table 1). In 2010, the American College of Veterinary Internal Medicine large animal consensus statement [2] listed several criteria for EMS based on available research data. The three main criteria included: documented or suspected insulin resistance (IR), that is hyperinsulinemia and/or abnormal glycemic and insulinemic responses to oral or IV glucose or insulin challenges; generalized obesity and/or increased adiposity in specific locations (regional adiposity) including the nuchal ligament ("cresty neck"), the tailhead, behind the shoulder, in the prepuce or mammary gland region; and predisposition toward laminitis that develops in the absence of other recognized causes, such as grain overload, retained placenta, colitis, colic or pleuropneumonia. Additional suggested components of the EMS phenotype included: hypertriglyceridemia, dyslipidemia, and increased low-density lipoprotein concentrations [6–8]; hyperleptinemia [9],

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Table 1
Parallels between MetS and EMS.

Human Metabolic Syndrome (MetS)	Equine Metabolic Syndrome (EMS)
Increased BMI or obesity	Generalized obesity assessed by body condition score (BCS)
Intraabdominal or visceral obesity	Regional adiposity in the nuchal ligament "cresty neck" phenotype strongly correlated with serum glucose, insulin, triglyceride and leptin concentrations, and glucose tolerance
Hyperinsulinemia	Hyperinsulinemia fasting insulin concentrations >20 mU/L
Impaired fasting glucose	Resting plasma glucose concentrations increased in comparison with normal horses in some studies
Insulin resistance	Insulin resistance suggested by various oral and IV glucose challenge models
Hypertension	Hypertension
Dyslipidemia increased NEFA, triglycerides, decreased VLDL, HDL	Increase in triglycerides, nonesterified fatty acids (NEFA), HDL cholesterol, decreased VLDL
Proinflammatory state (increased TNF-α, IL-1, IL-6)	Increased TNF-α, IL-1, decreased IL-6
Altered adipokines (increased leptin, decreased adiponectin)	Increased leptin, decreased adiponectin

Abbreviation: BMI, body mass index; HDL, high-density lipoprotein; IL, interleukin; TNF, tumor necrosis factor; VLDL, very-low-density lipoprotein.

arterial hypertension [10,11], altered reproductive cycling in mares [12,13], and increased systemic markers of inflammation in association with obesity [14].

Despite this consensus, our understanding of EMS pathophysiology and the risk factors associated with laminitis are still in their infancy. Furthermore, the features that define EMS are a subject of ongoing debate in the veterinary community. Descriptions of the metabolic phenotype of laminitis-prone horses and ponies have varied among published studies (Table 2) [6,8,10,11]. This lack of consensus between reports may be a symptom of study design: for example, unmeasured explanatory variables, insufficient sample size to detect significant effects in the presence of confounding variables, and differences in experimental design including differences in test cohort, breed, or time of sample collection (time of day and/or season). However, this lack of consensus also likely reflects the complexity of the "EMS" phenotype. What has become increasingly clear is that the relationships between the primary phenotypic features and key diagnostic measurements used in clinical and research settings are complex. The metabolic phenotypes routinely measured (e.g., insulin, insulin responses, adipokines, adiposity, and so forth) are highly influenced by the environment and vary due to physiologic factors such as age, breed, and sex, even in normal individuals. Furthermore, not all components of the syndrome (e.g., obesity) may be present in individuals with underlying metabolic derangements. The variability in biochemical measurements and inconsistency in clinical signs between individuals at risk for laminitis makes it difficult to establish clear diagnostic criteria or a consensus phenotype.

A better understanding of EMS pathophysiology requires a more clear phenotypic definition of EMS; a better grasp of the effects of both intrinsic and extrinsic factors that influence metabolic phenotype and phenotypic measures; and an appreciation of the complex interactions between the phenotypic components of the syndrome and the proposed risk factors. In this review, we will summarize the understanding of the EMS phenotype and propose a complex disease model that may help explain the variability in this phenotype.

2. Current Understanding of the EMS Phenotype

2.1. Insulin Resistance and Hyperinsulinemia

Although our understanding of the etiology and pathophysiology of EMS is far from complete, it seems likely that IR and/or associated hyperinsulinemia play an

Table 2
A summary of findings related to obesity, regional adiposity, and endocrine or metabolic variables in published studies of the equine metabolic syndrome (EMS) phenotype.

	Treiber et al 2006[a]	Frank et al 2006	Bailey et al 2008	Carter et al 2009[a]
Breed(s)	Welsh and Dartmoor ponies	Six breeds	Mixed-breed ponies	Welsh and Dartmoor ponies
Sample size	160	12	80	74
Obesity (BCS) in EMS suspects	Yes	Yes	No	Yes
Regional adiposity in EMS suspects	Yes	Yes	No	Yes
Hyperinsulinemia in EMS suspects	Yes (21.6 vs. 10.7 mU/L)	Yes (50.5 vs. 9.1 mU/L)	Yes[b] (69.5 vs. 21.5 mU/L)	Yes (20.5 vs. 8.8 mU/L)
Insulin resistance in EMS suspects	Yes (RISQI)	Yes (CGIT)	Yes[b] (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[b] (0.55 vs. 0.38 mmol/L)	Higher in EMS (53.0 vs. 39.0 mg/dL)
NEFAs	Not different	Higher in EMS (366.5 vs. 197.1 μmol/L	Not evaluated	Not evaluated

Abbreviations: BCS, body condition score; RISQI, reciprocal of the square root of the serum insulin concentration; CGIT, combined glucose-insulin tolerance test; NEFAs, nonesterified fatty acids.
[a] Data obtained from the same population of Welsh and Dartmoor ponies.
[b] Serum insulin and triglyceride concentrations and RISQI differed between ponies with and without a history of laminitis in summer but not in winter.

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