**Equine metabolic syndrome – what do we know now?**

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*Updates on pathophysiology and epidemiology of insulin dysregulation and insulin resistance, the role of genetics, obesity and physical activity.*

**Introduction**

The original ACVIM consensus defined equine metabolic syndrome (EMS) in 2010 as a syndrome of obesity, insulin resistance (IR) and laminitis. However, since then, research evidence has changed our understanding of the syndrome. EMS is a collection of risk factors for the development of endocrinopathic laminitis. The central defining pathophysiological feature is insulin dysregulation. While obesity is an important risk factor, obesity and lipid dysregulation, as well as cardiovascular and other features are not consistently found with the syndrome.

The aims of this presentation are to:

1. Discuss the pathophysiology of EMS focusing on the central feature of insulin dysregulation and how it might develop.
2. Discuss the other risk factors associated with EMS including obesity and lipid dysregulation. Recent research from the USA on new research into the genetic risk factors will also be discussed.
3. Discuss the history and epidemiology of EMS, including research from Australia on hyperinsulinaemia in ponies and new research form the UK looking at the prevalence and risk factors for EMS.

EMS was first described in 1999, as “Laminitis, Hypothyroidism and Obesity: a peripheral cushingoid syndrome in horses”.1 EMS was subsequently defined in the 2010 ACVIM consensus statement.2 It was described as a phenotype of obesity (regional or generalised), insulin resistance (hyperinsulinemia or abnormal insulin and glucose regulation; now known as insulin dysregulation [ID]3) and a predisposition to laminitis that has developed in the absence of recognised causes such as grain overload, colic, colitis, or retained placenta. 2 This definition was useful in encapsulating what was known about EMS at the time although it is also important to realise the significance of these three factors in producing the clinical phenotype.

*Obesity*: Obesity represents an important risk or predisposing factor for EMS, especially in highly susceptible breeds like UK native pony breeds where there is an underlying predisposition. However, obesity does not define EMS, and many ponies and horses are obese with normal insulin sensitivity and, conversely, some EMS horses and ponies have no external evidence of obesity.

*Insulin dysregulation*: Insulin dysregulation is central to EMS and the pathogenesis of laminitis has been shown to be closely associated with hyperinsulinemia in experimental models, field studies, and clinical studies (see presentation “Endocrine laminitis): Insulin dysregulation manifests as resting or basal hyperinsulinemia or an abnormal insulin response to oral or IV carbohydrate (non structural carbohydrate or NSC) challenge. 3 Some animals with EMS show a relatively greater response to oral NSC challenge than IV, which is of particular concern for these animals as a risk factor for laminitis. Either way insulin dysregulation is now considered the core defining factor in EMS.

*Predisposition to laminitis*: The most important disease expression associated with EMS in horses is laminitis. Despite a general acceptance by veterinarians of the existence of subclinical laminitis and corresponding gross changes in the hoof capsule (divergent rings, dropped sole, separation of the white line and cap horn production),histological evidence of this was only recently published from naturally occurring cases. 4

**Pathophysiology of EMS**

*Insulin dysregulation:* is the key feature of EMS. This term was first introduced by Frank and Tadros in 2014 3, and refers to any combination of 3 abnormalities:

1. Tissue insulin resistance (the inability of tissues to respond appropriately to insulin)

2. Basal hyperinsulinaemia

3. Postprandial (post carbohydrate) hyperinsulinaemia.

Insulin resistance is defined as a failure of tissues to adequately respond to circulating insulin. Insulin has many roles, the most important being to maintain euglycemia by rapidly and dramatically increasing glucose uptake into cells via translocation of GLUT 4 transporters to the cell membrane in response to hyperglycaemia. However, insulin is also involved in protein, fat and glycogen synthesis, endothelial activation, growth and gene expression (mitogenesis).

Insulin resistance can be classified as compensated or uncompensated based on glucose homeostasis. Compensated insulin resistance refers to the condition where the pancreas is able to respond to the peripheral insulin resistance by producing more insulin, resulting in a compensatory hyperinsulinemia and the ability to maintain euglycemia. Uncompensated insulin resistance occurs when the pancreas is no longer able to produce enough insulin, resulting in failure to maintain glucose homeostasis and hyperglycaemia or type 2 diabetes. Horses most commonly have compensated insulin resistance and rarely do they get pancreatic exhaustion and type 2 diabetes.3

The actions of insulin are mediated through activation of insulin receptors on target cells. The insulin receptor is linked to a number of key intracellular signalling pathways including mitogen activated protein kinase (MAPK) pathways, the phosphoinositide 3-kinase (PI3-kinase)/Akt mediated pathway and the AMP-activated protein kinase pathway, all of which are involved in metabolic regulation. As discussed in “endocrinopathic laminitis” we now know that insulin resistance is not a failure of insulin to interact with target cells, but altered intracellular signalling following binding of insulin to the insulin receptor. Alteration in the signalling of these pathways, in particular a dominance of signalling via the MAPK pathway, have been shown to be central to insulin resistance and subsequent metabolic dysfunction including dyslipidaemia, vasculopathy and coagulopathy in murine models and in man. 5

The third factor in insulin dysregulation is inappropriate post prandial or post NSC challenge hyperinsulinaemia. In all horses, glucose administered orally results in a greater insulin response compared to equivalent dose administered intravenously. The presence of glucose in the intestine stimulates the secretion of gut-derived hormones called incretins including glucagon-like peptide 1 and glucose-dependent insulinotropic

peptide, which stimulate the pancreas to secrete a greater amount of insulin than it would in response to the absorbed glucose alone. This mechanism is termed the enteroinsular axis. Incretin derived hyperinsulinaemia can be exaggerated in some horses with ID. 3 Whether or not hyperinsulinaemia is also exacerbated by reduced clearance is not yet clear. 3

*Development of insulin dysregulation:* What stimulates such profound persistent insulin dysregulation in EMS is currently unknown, but it is clear from evidence to date that there is not a simple causal relationship. In people with metabolic syndrome, three pathophysiological processes have been implicated in development of clinical complications of insulin resistance in people: glucotoxicity, lipotoxicity and inflammation.5

Whether or not these same factors apply to the horse is less well known. Certainly due to better preserved glucose regulation and the rarity of pancreatic exhaustion, the role of glucotoxicity appears to be less important in horses with EMS than in humans with metabolic syndrome and type 2 diabetes. Elevated levels of free fatty acids are a major factor contributing to insulin resistance and also have a direct effect on vascular dysfunction in people. In horses, elevated triglycerides have been measured in laminitis prone ponies with insulin resistance 6 and associated with hyperinsulinaemia in ponies. 7 Although inflammation is considered to be the central mechanism in both induction of insulin resistance and its effects in people, evidence for an association between obesity and inflammation in horses remains limited and conflicting.

In support of obesity inducing a pro-inflammatory state in horses, increased circulating tumor necrosis factor-α (TNF-α) concentrations, as well as increased interleukin-1 (IL-1) and TNF-α blood mRNA expression, were associated with increased BCS and body fat composition, in an age dependent fashion in mares. 8 These inflammatory cytokines can alter skeletal muscle response to insulin. For example, TNF-α has been shown to inhibit the action of insulin on skeletal muscle and IL-6 decreases insulin-dependent glucose uptake by skeletal muscle. There is also evidence of differential cytokine production between different adipose tissue sites in horses. Specifically, increased TNF-α protein expression has been found in visceral adipose tissue collected from insulin resistant horses 9 and increased mRNA coding for interleukin-1β and IL-6 has been found in neck crest fat. 10 However, inflammatory cytokines measured systemically or in the skeletal muscle were in fact decreased in obese hyperinsulinemic horses compared to controls in another study.11 It is therefore clear that further research is needed before we fully understand the links between obesity, inflammation and the development of insulin dysregulation.

*Lipid Dysregulation*: There has been much research looking at hormones and pro-inflammatory cytokines (collectively called “adipokines”) released from adipose tissue in man and laboratory animals. The most important adipokines are leptin and adiponectin. Leptin is a satiety factor, in the normal situation signalling the brain that the animal has ingested adequate energy. Leptin is important in modulating feed intake and thus regulation of body weight. However, leptin resistance results in defects in these signals and an increase in appetite. Hyperleptinemia associated with leptin resistance has been demonstrated in humans and horses with insulin resistance. 7,12 The relationship between insulin and leptin is complex but insulin appears to be an important factor in stimulating leptin secretion from adipocytes and leptin resistance often accompanies insulin resistance. Adiponectin is an insulin-sensitising adipokine that is also thought to have anti-inflammatory properties. The concentration of circulating adiponectin has been found to be inversely proportional to body fat mass in humans and horses.13 Low total adiponectin has been more recently associated with an increased risk of laminitis in ponies. 14

**Epidemiology**

From our understanding in laboratory animals and people the two key epidemiological factors in EMS are genetics and environment.

*Genetics:* It is likely that genetics is a crucial factor involved in EMS in certain breeds of horses, especially UK and Irish ponies, however, a full understanding of the genetic links in horses is yet to be elucidated. Of the spontaneously occurring cases of laminitis associated with insulin resistance or hyperinsulinemia recorded in the literature, there is a predominance of UK and Irish pony breeds and these breeds were significantly more likely to have endocrinopathic laminitis that cold blooded horses or Nordic ponies. 15 Treiber et al. 16 suggested a genetic basis for predisposition to pasture-associated laminitis, although only studied a single closed herd. This has led some to propose that there may be an evolutionary advantage to insulin resistance allowing these horses to survive in harsh conditions where they must maximise their glucose uptake from a poor diet (“thrifty” genotype), although the real situation is likely to be more complex with behavioural, genetic and epigenetic factors all contributing. Recent research from the USA is starting to tease out some of the genetic links to EMS. 17,18

*Environment:* The main environmental influences associated with the development of insulin resistance are obesity and a sedentary lifestyle. Obesity is a common problem in horses across the developed world. In Scotland, researchers found a 45% prevalence of obesity in non-competition horses and ponies. 19 In Virginia, USA, 32% were over conditioned (body condition score (BCS) 7-8/9) and 19% obese BCS 9/9. 20 However, not all obese horses have EMS and obesity was not a risk factor for hyperinsulinaemia in Australian ponies or pasture-associated laminitis in British ponies. 7,14 As well as generalised obesity, regional obesity may be important in the development of EMS.

The prevalence of insulin dysregulation in the general population probably depends on the breed sampled. Research from Australia in ponies has shown the prevalence of hyperinsulinaemia to be as high as 27% in pony breeds, including the Welsh Mountain pony and cob, Shetland, Connemara ponies. 7 Risk factors for the condition included increasing age and supplementary feeding. Work being undertaken by the author and colleagues in the UK has shown a prevalence of EMS in pony and cob breeds similar to the Australian study, 7 depending on the cut off used.

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