**Endocrine Laminitis**

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*Current concepts related to the pathophysiology of endocrinopathic laminitis including the hyperinsulinaemic model and naturally occurring cases.*

**Introduction**

Recent research has stratified the causes of laminitis in horses into 3 main categories:

1. *(Systemic)* *Inflammatory* caused by systemic diseases accompanied by clinical indicators of endotoxaemia (systemic inflammatory response syndrome or SIRS), including enterocolitis, pleuropneumonia, retained fetal membranes or grain overload;
2. *Weight bearing* laminitisand;
3. *Endocrinopathic* laminitis, associated with pituitary pars intermedia dysfunction (PPID) or Equine Metabolic Syndrome (EMS). Common to both these conditions are disturbed glucose and insulin regulation and, most importantly, the development of insulin dysregulation which in the horse is manifest as hyperinsulinaemia.

Endocrinopathic laminitis has been shown to be the most common cause of laminitis presenting primarily as lameness from laminitis rather than secondary to presenting for acute severe illness and hospitalisation. There are two main conditions associated with endocrinopathic laminitis:

1. Pituitary pars intermedia dysfunction (PPID) or;

2. Equine Metabolic Syndrome (EMS).

Common to both these conditions appear to be disturbed glucose and insulin regulation and, most importantly, the development of insulin dysregulation which in the horse is manifest as hyperinsulinaemia either basally, or in association with the ingestion of carbohydrates in forages and feeds.

The aims of this presentation are to:

1. Outline what we know about the relationship between insulin and laminitis, including what we have learned from field studies and the experimental model of hyperinsulinaemia developed in Australia.
2. Discuss what we have learned from the histology of endocrinopathic laminitis.
3. Outline how the above has led to new hypotheses as to how endocrinopathic laminitis occurs.
4. Discuss the clinical implications of this knowledge.

**The relationship between insulin and laminitis**

It is now well established that hyperinsulinemia associated with insulin dysregulation causes laminitis in affected horses, especially when challenged by dietary non-structural carbohydrates (NSC). Laminitis has been linked to insulin resistance and hyperinsulinaemia in field studies since the 1980’s. 1-3 Experimental research conducted in Australia has shown a direct link between hyperinsulinaemia and laminitis. 4,5 The research involved development of a hyperinsulinaemic model of laminitis and resulted in laminitis occurring in 100% of normal ponies or horses exposed to high concentrations of insulin (> 1000 µIU/ml) while maintaining euglycaemia of 5 mmol/l using a modified euglycaemic-hyperinsulinaemic clamp technique. All treated ponies or horses were healthy, young and non-obese, with no history of laminitis and no evidence of endocrine or other abnormalities on blood tests. Laminitis occurred slowly and in all 4 limbs, with the onset of lameness associated with laminitis (Obel grade 2) by approximately 48 hours. There was no evidence of gastrointestinal involvement or systemic illness throughout the experiments. 4,5 Furthermore, histological lesions of laminitis have been detected as early as 6 hours post exposure to hyperinsulinaemia, 6 and in response to much lower circulating concentrations of endogenous insulin produced in response to glucose infusion resulting in moderate hyperglycaemia. 7

The hyperinsulinaemic model of laminitis has allowed us to explore different mechanisms possibly involved in the development of endocrinopathic laminitis. Systematic research has excluded glucose deprivation 8 and glucose excess. 9 Despite their upregulation in naturally occurring and induced models of systemic inflammation, 10 metalloproteinases (MMP2 and MMP9 and ADAMTS4), this not been observed in hyperinsulinaemic laminitis where minimal MMP or ADAMTS4 activity during the developmental and acute stages of laminitis occurred and only MMP9 upregulated at later stages of laminitis (48 hours), correlating with histological evidence of neutrophil infiltration. 11

More recently insulin’s effect on signalling within cells (intracellular signalling pathways), and its effects on blood flow have provided important mechanistic clues. Insulin, when it is working via its appropriate intracellular pathways has marked effects on the vascular endothelium, stimulating vasodilation via nitric oxide mediated pathways in both small and large vessels. Insulin dysregulation results intracellular pathways being altered and ultimately the opposite effect, causing vasoconstriction.

Recent research in horses has confirmed both the rapid induction of insulin dysregulation from hyperinsulinaemia, and an abnormal vasoconstrictive response to insulin in vessels. Ex-vivo vascular ring models in the horse showed that just 30 minutes pre-incubation in insulin resulted in inappropriate vasoconstriction response to the addition of insulin. 12 This effect was reversed by blocking the inappropriate intracellular pathway of insulin signalling. Further work using ex-vivo lamellar vasculature of normal horses 13 and ex-vivo digital and facial vessels of horses with naturally occurring endocrinopathic laminitis 14 has supported this first study.

However, while we know this is occurring in the vasculature, we also know from examining lamellae histologically that the earliest lesions are associated with a loss of epithelial cell integrity and stretching. The current theory of endocrinopathic laminitis is these lamelllar epithelial cells are affected by hyperinsulinaemia, just like the vascular endothelial cells were shown to be affected above, resulting in abnormal intracellular pathways being activated in insulin dysregulated horses. This results in cellular damage and disruption of cytoskeletal organisation, allowing these cells to stretch under mechanical forces, ultimately leading to laminitis. 15

**Histology**

As early as 6 hours post exposure to hyperinsulinaemia or after or 48 hours of hyperglycaemia, marked elongation of the secondary epidermal lamellae is observed. 6,7 Cellular changes dominated by altered orientation and shape, stretching then apoptosis and mitosis precede the pain and inflammation of Obel grade 2 laminitis. Histopathology is less severe and fewer inflammatory cells infiltrate than laminitis caused by systemic inflammatory diseases or carbohydrate overload models. In both experimental hyperinsulinaemia and in naturally occurring endocrinopathic laminitis the lesion is not basement membrane driven as has been proposed from research in inflammatory models. Early cellular changes are associated with limited and quite localised basement membrane damage likely to be associated with the cytoskeletal disruption within the epithelial cells. 15

The histology of naturally occurring laminitis is similar to the hyperinsulinaemic model and shows a range of lesions with overall stretching and lengthening of primary and secondary lamellae. Abaxially (underneath the hoof wall) there is apoptosis, lamellar fusion and hyperplasia, keratinisation sometimes leading to tearing and separation. Axially (adjacent to P3) there is tapering of the primary and secondary lamellae in a variable amounts. 16

A key finding from studying naturally occurring cases of endocrine laminitis was that the histological findings did not match with the duration of laminitis emphasising a prolonged subclinical phase. Putting these findings together (the early lesions in the model and the evidence of subclinical lesions in the naturally occurring cases) supports the contention of laminitic rings being the hallmark of subclinical laminitis and an early warning sign of endocrinopathic laminitis.

**Clinical Implications**

Our approach to laminitis has changed substantially in the past decade due to shifts in our understanding of the clinical syndrome and its causes. The main changes for laminitis of endocrine originas have been dictated by 3 facts:

1. Endocrinopathic laminitis is the most common form of laminitis presenting primarily as laminitis; 17,18
2. Endocrinopathic laminitis is directly caused by hyperinsulinaemia; and
3. Diagnosis of and management of insulin dysregulation is essential to manage laminitis effectively as well as to prevent recurrence.

This has implications for diagnosis, treatment and long-term management of laminitis. For laminitis that presents as the primary problem in a horse that is not systemically unwell, and that is not non-weight bearing for another reason, it should be assumed that the laminitis is due to an endocrinopathy. Appropriate testing should be carried out according to the signalment of the horse. Specifically check if the horse has EMS, PPID or both. If you are unable to reach a diagnosis, check your test and re-test, or use a more sensitive test. Remember for EMS think insulin not obesity – not all obese horses are endocrinologically abnormal.

The importance of using an understanding of endocrinopathic laminitis and the lesions that occur, especially the relationship of laminitis with insulin dysregulation cannot be overemphasised. Management should be guided by monitoring of insulin dysregulation not simply pain and grossly visible radiographic or hoof capsular changes, otherwise pathological changes to cells can be continuing to damage the feet ultimately causing recurrence or treatment failure.

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