Endocrinopathic Laminitis — How is it different?
Eleanor M. Kellon, VMD
Owner, Equine Nutritional Solutions; Staff Veterinary Specialist, Uckele Health and Nutrition; Owner, ECIR Outreach Group; Veterinary Advisor, ECIR Group Inc.

Endocrinopathic laminitis is hormonal/metabolic laminitis related to a pathology in the endocrine system. There are striking differences between laminitis caused by the hormonal disruption of insulin and that caused by other factors.

Understanding what endocrinopathic laminitis is begins with understanding what it is not.

Historically, the known or suspected causes of laminitis have been described as:

- “Lush pasture”.
- Carbohydrate overload in the form of grain.
- Black walnut toxicity.
- Immunologic vasculitis such as Strep equi.
- Endotoxemia — probably a form of Systemic Inflammatory Response (SIRS) caused by different types of bacteria. Most common are Salmonella, Clostridia, Potomac Horse Fever, and retained placenta.
- Some plants like Hoary Alyssum.
- Excessive weight bearing (“supporting-limb laminitis”).

Over the last 15 years, attention has slowly but inexorably been turning to insulin as causal. A historic overview of research that was prescient includes:

- Robie, et al., 1975: Ponies less insulin sensitive than Tb; Morgan in between.1
- Coffman & Colles, 1983: Chronically laminitic ponies are Insulin Resistant (IR) compared to normal ponies.2
- Field & Jeffcott, 1989: Fat laminitic ponies have higher insulin response to glucose.3

None of these studies made it into veterinary school teaching at the time.

In 1999, farrier Henry Heymering and I did a field study that showed a positive response to magnesium supplementation. Chronic cases of laminitis were very common, but no one knew how to help these horses. Epsom salt use in the UK had been reported to favorably affect horses before laminitis starts, while they have laminitis, and even in chronic cases. We gave magnesium to Henry’s clients’ laminitic horses and saw pain relief with the crest and fat deposits going down.

Looking over the literature at that time, a possible connection was found to what was being described as “Syndrome X”, known now as metabolic syndrome. Today we have over 1,000 studies looking at magnesium status in humans with insulin resistance (IR). It is well proven in people that poor magnesium status predisposes IR, while correcting improves it.
In 2002, Johnson proposed the existence of equine metabolic syndrome/peripheral Cushing’s. It was the first suggestion that IR may exist as a pathology outside of Pituitary Pars Intermedia Dysfunction (PPID). At this point it was theorized that IR was caused by peripheral overproduction of cortisol. No one looked at the studies referenced above that horses could vary as to their insulin sensitivity, nor did they think of it as an issue.

“Equine Metabolic Syndrome” was not widely accepted by the veterinary community in 2002. There were many highly critical of Johnson. Skeptics were also on the Equine Cushing’s group when I first joined in 2001, but by 2002, we were united and delighted to see the affirmation from Johnson’s paper that IR can indeed exist.

In 2006, with the publication of Treiber, et al., her field study showed IR to be an accurate predictor of the risk of pasture-associated laminitis. The laminitis risk correlated with a growth flush of clover in the field with no change in fructan and no change in cortisol. There was, however, a huge jump in insulin.

In 2007, Asplin, et al., reported inducing laminitis in ponies by insulin intravenous infusion. Blood glucose was maintained by a simultaneous glucose infusion. Within 24-48 hours this caused ponies to become laminitic. In 2010, de Laat successfully repeated this in Standardbred horses, a breed known to be insulin sensitive.

Once accepted, hyperinsulinemia shot to the top of the list for causing laminitis. Karikowski, et al., 2011 reported that 89% of laminitis cases had an endocrine pathology. When considering that 10-15% of a given population will have laminitis, one can appreciate how sizable this problem is: 10 million horses in the US now would offer one million cases per year.

**Typical Scenarios Have a Common Thread: Insulin**

**Steroids**

Practicing veterinarians had also long suspected a link between administration of corticosteroid drugs and laminitis. Interestingly, the risk is great enough for the FDA to require a laminitis warning on corticosteroids for equine use. There was a disconnect between the adverse drug reaction reports in clinical experience vs. experimental efforts to induce laminitis with corticosteroids. Researchers could not induce laminitis under experimental conditions.

Corticosteroids have since been found to potentiate contraction responses to epinephrine, serotonin, and norepinephrine in digital veins, with a more pronounced reaction to vasoconstrictors.

Multiple studies confirm that corticosteroids induce insulin resistance in horses, as they do in other species.

There is a higher risk of laminitis with PPID/IR horses and those drugs with long-acting, high glucocorticoid (anti-inflammatory) activity. There is a lower risk with non-IR horses and short-acting, low glucocorticoid activity. Dexamethasone, Betametasone, Triamcinolone with higher anti-inflammatory effect have a higher risk than prednisone. (Figure 1)

![Figure 1. Relative potencies of adrenal steroid. basicmedicalkey.com](basicmedicalkey.com)
Does oral prednisolone treatment increase the incidence of acute laminitis? In a 13-year retrospective study, Jordan, et al., 2017, found no increased risk of laminitis with oral prednisolone.

**Laminitis in Pregnancy**

It is well recognized that pregnant mares are at increased risk of laminitis, crossing all breeds. All mares are at risk. Is the cause obesity or hormonal?

George, et al., 2011, looked at 22 pregnant and 10 nonpregnant mares, all on the same hay and pasture diet. Frequently Sampled Intravenous Glucose Test (FSIGT) testing showed pregnant mares had delayed glucose clearance and higher insulin, the definition of insulin resistance.

Whether the cause is PPID, cortisol/corticosteroids, or pregnancy, all hormonal incidences/situations that link to laminitis boil down to insulin resistance as a common denominator.

**Mechanism of Endocrinopathic Laminitis**

HOW does insulin resistance result in laminitis? Our information is still incomplete. We have more understanding of what the pathophysiology of Endocrinopathic Laminitis is not, than what it is.

What is the normal physiology of this tissue and what goes wrong in laminitis? We don’t even know enough about what goes on in this tissue in normal states, so it is hard to know what to look for in disease states. The information is definitely incomplete. While we know almost nothing about what is going on with tissues in this state, we do know what is NOT.

**Candidates for Mechanisms From the Study of Other Causes of Laminitis**

**Carbohydrate or Fructan overload**

The normal anatomical characteristics that are assessed before allocating a laminitis grade to a section of lamellar hoof tissue are as follows (Figure 2):

- The tips of the secondary epidermal lamellae (SELs) are always rounded (club-shaped) and never tapered or pointed.
- The basal cell nuclei are oval in shape with the long axis of the oval at a right angle to the long axis of the secondary epidermal lamella. These parameters can be satisfactorily assessed using routine haematoxylin and eosin (H&E) staining of sections.
- The basement membrane penetrates deeply into the crypts between the SELs and outlines the wafer-thin, but connective-tissue filled, secondary dermal lamellae. The basement membrane is tightly adherent to the basal cells of each SEL.

![Figure 2. Histological stages of laminitis in carbohydrate overload. Equine Laminitis, Christopher C. Pollitt, BVSc, PhD.](image-url)
White blood cells invade the lamina in the inflammatory state.

**Basement Membrane Pathology**

The basement membrane is a thin layer of connective tissue between the secondary epidermal laminae (SEL) and the Secondary Dermal Laminae (SDL), which in some theories of laminitis is affected, causing lamellar separation.

**Enzymatic Theory of Laminitis**

The enzymatic theory of laminitis pertains to grain/fructan overload, or any hind-gut model of laminitis, where the initiating event leading to break down and separation of the epidermal laminae from the basement membrane is activation of metalloproteinases MMP-2 and MMP-9 proteolytic (protein-dissolving) enzymes by a circulating factor such as Streptococcus bovis toxin in carbohydrate overload. The theory is that the toxin is absorbed in large amounts and reaches the feet, activating MMP enzymes, which break down the basement membrane. We do not know why the MMP activation is limited to the feet but it may be related to unique regulation of activity in this tissue where MMP activity is high and necessary to allow the hoof wall to grow down.

Batimistat is an MMP inhibitor that proponents believed could stop/block MMP, and has been shown to work in vitro. Field trials of Batimastat were being conducted in 2008 in field laminitis cases. No further reports on effectiveness have been released in the subsequent 10 years.

**Leucocyte Infiltration and MMP Activation**

A twist on the MMP theory is that MMPs are actually activated as part of an inflammatory cascade that is initiated by white blood cell migration into the laminae. These cells and MMPs are invading the tissue, presumably in response to mechanical tissue break down; however, no cause of this initial mechanical breakdown event has been given.

This neutrophilic infiltration is a feature of hind-gut initiated laminitis and is seen with black walnut laminitis, as well.

**Endocrinopathic Laminitis Is Different**

**Pathophysiology — MMP activation**

The histology with hyperinsulinemia is most notable for what we do not see compared to other types of laminitis. The same elongation of SEL occurs as with other types of laminitis, but much earlier in the event and very quickly — as early as within the first 24 hours. There is also no basement membrane damage or WBC infiltration.

In 2011, de Latt showed that the developmental and acute phases of insulin-induced laminitis involve minimal metalloproteinase activity. Induced hyperinsulinemia caused no change in MMP-2, MT1-MMP, TIMP-3 and ADAMTS-4. All the enzymes you would expect to see in inflammatory response were just not there. MMP-9 was increased, but only in an inactive form, which may have come from white cells in the area that actually secrete the inactive form.

**Pathophysiology – Glucose Deprivation**

French and Pollitt, Equine Vet J 2004 noted that laminar explants cultured without glucose developed a
failure of basal cell cytoskeleton and loss of connections under tension. However, all cells need glucose to survive so the findings were not surprising. It was theorized that insulin resistance was depriving the cells of glucose but Asplin, et al., in 2011\textsuperscript{21} showed that those cells don’t require insulin.

Expression of GLUT4, the insulin dependent glucose transporter, is absent to barely detectable in coronary band and lamellar tissue, consistent with epithelial tissue.

To say the cells died from insulin resistance and glucose starvation is impossible.

**Pathophysiology — IGF-1**

Insulin-like Growth Factor-1 (IGF-1) is an anabolic protein produced by the liver in response to Growth Hormone. It is called “insulin-like” because it “looks like” insulin, but it does not behave like insulin. It is the active form of Growth Hormone.

Because it is structurally similar to insulin, IGF can bind to insulin receptors; but in studies in other species, the binding strength is 100 to 1,000 times weaker than insulin.

The IGF-1 theory is that insulin binding to IGF-1 receptors causes over-proliferation of the SEL\textsuperscript{22}. A frequent split of cells is seen in the tissues with high insulin and is unique to endocrinopathic laminitis. (Figure 3) IGF1 and cells are being stimulated to reproduce for some unknown reason — perhaps tissue trauma.

However, high insulin level caused down-regulation of IGF-1 receptors in the laminae within 24-46 hours. This down-regulation is counterintuitive as it is not what you would expect to see; however, it does prove that the insulin, at least, affects those receptors.

In another study, induction of hyperinsulinemia by diet or infusion induced an increase in IGF-1-related signalling proteins in lamellar biopsies\textsuperscript{23}.

These are all bits and pieces of incomplete information. Is increase in IGF-1 signaling the cause of the laminitis or a response to tissue damage? With IGF-1, we just don't know yet.

**Pathophysiology — Vascular**

The most well-described pathology in endocrinopathic laminitis is the vascular problems. We know endothelin-1, the most potent vasoconstrictor known, is increased. It is know to be high in IR horses and high in the feet of endocrinopathic horses. Nitric oxide is a natural antagonist of endothelin-1. In a normal cell there is a balance between nitric oxide production and endothelin-1, but in the IR horse, the endothelin-1 is prevalent.

When insulin was infused into isolated capillaries of the feet postmortem (Gauff, et al., 2014\textsuperscript{24}), researchers found that ETR-A (endothelin receptor) staining increased significantly with insulin perfusion, implicating endothelin. Mean ETR-A staining intensity for capillaries and small vessels was significantly (p<0.001) higher in lamellar tissues with insulin perfusion. ETR-A staining intensity of deep dermal veins and arteries was also significantly higher with insulin perfusion. Lamellar ETR-B blood vessel staining intensity was also higher.
ETRs were also identified on keratinocytes — the cells producing the lamina tissue — possibly with more density at lamellar tips. ETRs cause proliferation in other species and endothelin is known to cause proliferation in other species. It might be the endothelin that is causing the cells to divide widely and more rapidly than they normally would, and not the IGF-1.

In Gauff, et al., 201326 (same model as above), they found that in addition to endothelin receptor activity being up, there was significantly higher vascular resistance, edema formation, and immunostaining for ET-1 in laminar tissues from insulin-perfused limbs from normal horses.

**Nitric Oxide**

Over 1,900 studies in humans and other species confirmed a reduced nitric oxide availability in insulin resistance. This is a major factor in microvascular disease and also has metabolic effects. Hemorrhages and onycholysis (loosening of the nail plate from the bed underneath it, Figure 4.) in humans is considered a manifestation of microvascular disease.

Berhane, et al., 200626 confirmed that nitric oxide is an important mediator of vasodilation in equine digital vessels.

Morgan, et al., 201627 documented a reduced response to vasodilators and an increased response to vasoconstrictors in both hoof vessels and facial artery. These changes due to high insulin are going on throughout the IR horse’s body.

**SUMMARY**

There are many gaps in what we know about endocrinopathic laminitis.

What it’s NOT:

- Not an inflammatory process — none of the studies have shown that.
- Not obesity related.
- Does not involve basement membrane disruption/MMP activation.
- Not related to impaired glucose uptake. Nutrition of the cells is not the issue.

What it IS:

Unique histopathology characterized by many mitotic figures. Not seen in other forms of laminitis.

- Triggered by hyperinsulinemia.
- There is a hyperproliferative effect related to IGF-1 or endothelin or ?
- Likely prominent circulatory component due to microvascular disease.
REFERENCES


25 Ibid.
