Understanding, diagnosing and managing endocrinopathic laminitis

Endocrinopathic laminitis (or hyperinsulinaemia-associated laminitis) is the most common type of laminitis encountered in equine practice. Strict attention to risk factors and early recognition and diagnosis of insulin dysregulation – as part of equine metabolic syndrome or pituitary pars intermedia dysfunction – greatly decreases the risk of hyperinsulinaemia-associated laminitis. Early treatment and a committed client, veterinary and farriery team is critical to improve the prognosis. Treatment of hyperinsulinaemia-associated laminitis should encompass a three-pronged approach: treat the underlying cause (insulin dysregulation associated with equine metabolic syndrome or pituitary pars intermedia dysfunction); give anti-inflammatories and analgesics; biomechanically support the foot. The field of equine endocrinopathic disease is very active, so it is important to stay up to date on potential diagnostics and therapeutics.

https://doi.org/10.12968/ukve.2024.8.1.14

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Key words: endocrinology | laminitis | imaging | management

Submitted: 8 September 2023; accepted for publication following double-blind peer review: 18 October 2023

Endocrinopathic laminitis, or hyperinsulinaemia-associated laminitis, is the most common form of laminitis affecting the equine population, accounting for almost 90% of clinical cases in horses and ponies (Karikoski et al, 2011). One-third of horses develop laminitis in their lifetime (Wylie et al, 2011) and, in spite of advances in diagnostics and therapeutics, it remains a top cause of euthanasia in horses. A study reviewing data from first-opinion UK veterinary practice records of 70 477 horses and ponies found an almost six-times higher mortality rate in those with a diagnosis of laminitis (in horses with at least two morbidities) compared to those with no chronic disease; 74% of cases with multiple morbidities that were euthanised had laminitis as one of their conditions (Welsh et al, 2016). While hyperinsulinaemia-associated laminitis has similarities to the other main types of laminitis (sepsis-associated and supporting limb laminitis), there are some specifics to the pathophysiology, presentation, diagnosis and treatment of hyperinsulinaemia-associated laminitis that are helpful to keep in mind when seeing these cases.

The diagnosis and treatment of both insulin dysregulation – as it relates to equine metabolic syndrome and pituitary pars intermedia dysfunction – and hyperinsulinaemia-associated laminitis are active areas of ongoing research because of the high prevalence of these conditions. Breeds native to the UK (such as Cob, draught-types, Welsh breeds, Shetland and Highland ponies) have a higher incidence of obesity than light-breed horses, which is a known risk factor for equine metabolic syndrome and laminitis (Stephenson et al, 2011; Robin et al, 2015). One study used a dynamic oral glucose test to identify a 23% prevalence of equine metabolic syndrome within UK breeds aged 3–14 years (Carslake et al, 2021).

First-opinion veterinarians are at the front line of prevention and treatment of hyperinsulinaemia-associated laminitis. A survey of veterinarians from the UK and USA found that two-thirds of 213 respondents had altered their diagnostic approach to laminitis since graduation, and about 40% of respondents had increased their use of diagnostics for equine metabolic syndrome and pituitary pars intermedia dysfunction (Rumfola et al, 2022). Prevention is far better than treatment because much lamellar damage has often occurred by the time there are clinical signs of laminitis (de Laat et al, 2013). Early recognition, coupled with appropriate diagnostics and treatment, is essential in improving the outcome for horses with hyperinsulinaemia-associated laminitis. This is a preventable form of laminitis in many instances, in particular if the team of client, caregiver, farrier and veterinarian works together, understands the risk factors and does what it can to mitigate them.

Defining hyperinsulinaemia-associated laminitis

Hyperinsulinaemia-associated laminitis is seen when sustained hyperinsulinaemia causes stretching, proliferation and elongation of the digital lamellae without damaging the underlying basement membrane. A key difference from other types of laminitis is that hyperinsulinaemia-associated laminitis is often insidious in onset, but usually eventually progresses to more classical signs of laminitis. While hyperinsulinaemia-associated laminitis can be seemingly acute in onset, these horses likely had underlying changes that went unnoticed until the 'severe' clinical episode.

Hyperinsulinaemia-associated laminitis is most commonly seen in horses with pre-existing insulin dysregulation associated with pituitary pars intermedia dysfunction or equine metabolic syndrome. It is a core part of the definition of equine metabolic syndrome, along with generalised or regional adiposity and insulin dysregulation (resting hyperinsulinaemia, post-prandial hyperinsulinaemia or tissue insulin resistance), and is detected in approximately 30% of horses with pituitary pars intermedia dysfunction (McGowan et al, 2013). Determining if pituitary pars intermedia dysfunction and insulin dysregulation are comorbidities, or if one leads to the other, is an active area of current research which will help drive future management options.

Occasionally, horses with minimal known risk factors can develop insulin dysregulation and subsequent hyperinsulinaemia-associated laminitis under specific circumstances, though often they likely had unidentified risk factors. For example, horses that develop hyperinsulinaemia-associated laminitis with pasture access (Menzies-Gow et al, 2017) and corticosteroid administration (Timko et al, 2022) likely have pre-existing unrecognised insulin dysregulation that is overwhelmed by additive risk factors such as high fructan intake and steroid-induced changes in insulin dynamics respectively. Even sepsis-associated laminitis may have an additive effect of insulin dysregulation associated with illness- or hospital-related stress (Tadros et al, 2013; Bertin et al, 2018).

Pathophysiology

In hyperinsulinaemia-associated laminitis, there is proliferation and stretching of lamellar cells that leads to loss of lamellar integrity, minimal evidence of local inflammation in the acute phase (as evidenced by leukocyte migration into the lamellar tissue), and concurrent potential adaptations in local metabolism and blood flow, all together culminating in failure of the suspensory apparatus of the third phalanx. This is in notable contrast to the underlying pathophysiology and described histological changes of sepsis-associated and supporting-limb laminitis, in which inflammation and blood flow play large roles (Asplin et al, 2010; de Laat et al, 2013; Karikoski et al, 2014).

Cases of hyperinsulinaemia-associated laminitis may present as an acute episode, but most often there are multiple episodes of subclinical lamellar damage until it reaches a threshold or has an overwhelming inciting event. The resultant clinical laminitis and severe lameness most often represents an acute exacerbation of a chronic (and/or subclinical) condition (Karikoski et al, 2015; de Laat et al, 2019).

The ability to induce Obel grade 2 laminitis with sustained hyperinsulinaemia (>1000 µIU/ml for 46–55 hours) is well described in the literature (Asplin et al, 2007). The reported insulin threshold in research settings is around 200 µIU/ml (de Laat et al, 2012), yet clinically it must vary dependent upon a host of individual factors, such as:

- Duration of hyperinsulinaemia
- Hoof quality
- Previous lamellar events
- Concurrent disease (for example those causing sepsis, support-limb lameness, presence of pituitary pars intermedia dysfunction).

The predominant hypothesis is that hyperinsulinaemia causes inappropriate stimulation of the insulin-like growth factor-1 receptor on lamellar epidermal cells, setting off a cascade of downstream events which results in the lamellar changes seen in hyperinsulinaemia-associated laminitis (Rahnama et al, 2021a). This theory is complicated by conflicting data on the binding of insulin-to-insulin receptors on insulin-like growth factor-1 receptors, but blocking insulin-like growth factor-1 receptors mitigates laminitis in hyperinsulinaemia induction models, supporting the underlying hypothesis (Rahnama et al, 2020; 2021b). There is also increasing evidence of metabolic dysfunction within the lamellae. For example, hyperinsulinaemia causes hypoaminoacidaemia, which in turn may contribute to the loss of lamellar epithelial cell adhesion, cell stretch and extracellular matrix degradation, as well as altered turnover of lamellar structural proteins seen with hyperinsulinaemia-associated laminitis (Stokes et al, 2019; 2021).

Laminitis is categorised into several phases and the author believes that the use of consistent terminology improves understanding of both the disease and treatment methodologies.

1. The developmental or subclinical phase: This occurs before any clinical signs are seen. During this time there is active lamellar injury (and treatments are most likely to be efficacious in arresting the process)
2. The acute phase: The onset of this phase coincides with the appearance of clinical signs and can last up to 72 hours or until there is displacement of the third phalanx in relation to the hoof capsule
3. The chronic phase: This occurs after any displacement of the third phalanx with respect to the hoof wall and can last months to years with stabilisation of the clinical signs.

Clinical signs

Clinical signs of hyperinsulinaemia-associated laminitis can be divided into those seen with chronic disease, signs seen during an acute episode or active flare-up (these are pain-related and may be super-imposed over chronic signs) and signs related to an underlying endocrinopathy. Most veterinarians can readily appreciate the signs of equine metabolic syndrome and pituitary pars intermedia dysfunction, ranging from the pathognomonic to the subtle. However, the more nuanced changes in the foot are not always readily apparent on physical exam unless the veterinarian is specifically evaluating for them.

Chronic signs related to hyperinsulinaemia-associated laminitis include divergent hoof rings that are wider at the heels (these

Figure 1. A hoof demonstrating divergent hoof rings indicative of chronic laminitis. Note the rings are wider at the heels (yellow arrow) than at the dorsal wall (black arrow).

Figure 2. The sole of a laminitic hoof, demonstrating stretching (asterisk) and bruising (black arrows) of the white line.

Figure 3. Chronic laminitis may lead to the development of an overgrown dorsal hoof wall, creating a 'slipper toe'.

take at least 3 months to develop; Karikoski et al, 2015) (*Figure 1*), stretching or bruising of the white line (this is most evident at the time of trimming, so farrier input is key) (*Figure 2*), soreness after shoeing or trimming (owner-reported) and deformation of an overgrown dorsal hoof wall creating a 'slipper toe' (*Figure 3*).

Signs of an acute episode of hyperinsulinaemia-associated laminitis are similar to other types of laminitis and include:

- Increased digital pulses in the affected limbs
- Reluctance to move
- Choppy or stilted gait
- Hypermetric gait (especially in the hind limbs – this can be confused with neurological disease)
- Sensitivity to hoof testers (especially over the toe, although this can have many false positive with up to 50% of non-laminitic horses having sensitivity) (Meier et al, 2019a)
- Visible or palpable oedema or ledging of the coronary bands (associated with sinking)
- In severe cases, more systemic signs of pain including tachycardia, tachypnoea, inappetence and depression.

Similar to other types of laminitis, hyperinsulinaemia-associated laminitis is more likely to clinically affect the forelimbs compared to the hindlimbs; however, it can affect all four limbs concurrently or, rarely, just one limb (typically, this is in combination with support limb laminitis).

The long-standing Obel laminitis grading system was modified and validated for clinical use in specifically monitoring cases of hyperinsulinaemia-associated laminitis (Meier et al, 2021) (*Table 1*). It is never necessary or appropriate to force an acutely laminitic horse to move for a lameness examination or to assign an Obel grade, because it causes more lamellar damage and makes the horse suffer needlessly. In addition, veterinarians should consider familiarising themselves with, and using, an objective pain scoring system at each veterinary visit when evaluating laminitis, and possibly training the caregiver to use it as well. Viñuela-Fernández et al (2011) reported good overall reliability for use of the visual analogue scale, Obel and clinical grading system to evaluate horses with clinical laminitis by video. While these scores have not been consistently validated for laminitic pain, the horse (facial) grimace scale or various composite pain scales can be readily incorporated into practice (de Grauw and van Loon, 2016), in conjunction with the modified Obel method. It is likely most important for a clinician to become comfortable with a scoring system and use it repeatedly to improve reliability.

Diagnostics

Radiographs

Similar methods can be used to obtain and interpret radiographs of the foot for hyperinsulinaemia-associated laminitis as for other types of laminitis. Place both front (or hind) feet on wooden blocks to raise them up off the ground, allowing acquisition of the solar surface of the foot (even if only one foot is of concern, the horse needs to be standing squarely on both blocks to normalise weight-bearing and it is helpful to evaluate the contralateral foot for a baseline, at a minimum).

It is helpful to mark the dorsal hoof wall up to the coronary band on the lateral views with a radio-opaque marker (use bar-

Table 1. Modified Obel grading system

Order of assessment	Criteria	Description	Possible score
1	Weight shift	No weight shifting Shifting weight between feet at rest	0 1
2	30-second foot lift	Prompt, willingly maintained Slow and maintained, but with struggle Unable to maintain lift or resists attempts to lift	0 1 2
3	Gait at walk	Normal Mild, short and stilted Moderate, short and severely stilted	0 1 2
4	Gait at trot (if possible)	Normal Pronounced short, stilted Unable to maintain trot	0 1 2
5	Gait at circle (if possible)	Normal Head rises when circling towards lame foot, Head rises circling either way	0 1 2
6	Movement	Moves willingly Reluctant to move	0 1
7	Digital pulse	Normal – difficult to palpate, not bounding Abnormal – bounding	0 1
8	Hoof testers	No response Positive response	0 1

(Meier et al, 2021)

ium paste (*Figure 4*) or tape on a piece of metal, or even a scalpel blade within its packaging). While digital radiology makes it easier to see the coronary band, the marker leaves no doubt. It is also helpful to either tape a radio-opaque marker of known length onto the dorsal hoof wall and/or incorporate one into the block. This allows for image calibration in the digital radiography software to improve measurement accuracy (*Figure 5*). It is critical to get good lateromedial radiographs, and ideal to also get dorsopalmar, dorsoplantar and solar margin views to evaluate the integrity of the third phalanx and to help the farrier balance the hoof (*Figure 6*; *7*; *8*). *Table 2* describes the common radiographic findings seen with laminitis, regardless of the cause.

In horses with an acute episode of hyperinsulinaemia-associated laminitis, the author feels that it is more common to see stretching or thickening of the hoof–lamellar zone and/ or signs of previous bouts of laminitis compared to horses with acute laminitis of other causes. The former is because of the underlying pathophysiology of hyperinsulinaemia-associated laminitis, and the latter because clients are unfortunately reportedly poor at recognising mild laminitis, and thus horses with insulin dysregulation can have repeated unnoticed mild episodes (Tadros et al, 2019). Logically and reportedly, signs of chronic laminitis on radiographs suggest a high likelihood of recurrence (de Laat et al, 2019).

Of note, the severity of clinical signs of hyperinsulinaemia-associated laminitis do not seem to correlate as well with radiographic changes as with other types of laminitis, likely as a result of the chronic nature of the disease (Sillence et al, 2022). Similarly, clinical signs may improve over the first couple of weeks without significant improvement in radiographic changes (Sillence et al, 2022).

Figure 4. Barium paste has been used to mark the dorsal hoof wall to the coronary band. This is easy to wipe off after the lateral radiographs, before taking the dorsopalmar and dorsoplantar views.

Diagnosing endocrinopathies

A full review of the diagnosis of equine metabolic syndrome and pituitary pars intermedia dysfunction is beyond the scope of this article and the author refers the reader to the biennial consensus statements on these topics by the Equine Endocrinology Group (available at: https://sites.tufts.edu/equineendogroup/) and the British Equine Veterinary Association primary care clinical guidelines: Diagnosis and management of equine pituitary pars intermedia dysfunction (Menzies-Gow et al, 2023). The recommended workup is summarised in *Table 3*, and some directed comments will follow here.

When evaluating a horse for active or risk of hyperinsulinaemia-associated laminitis, evaluate the body condition score (with the client present, so they learn how), take photos of the horse from all sides for future comparison, use a weight tape (use the

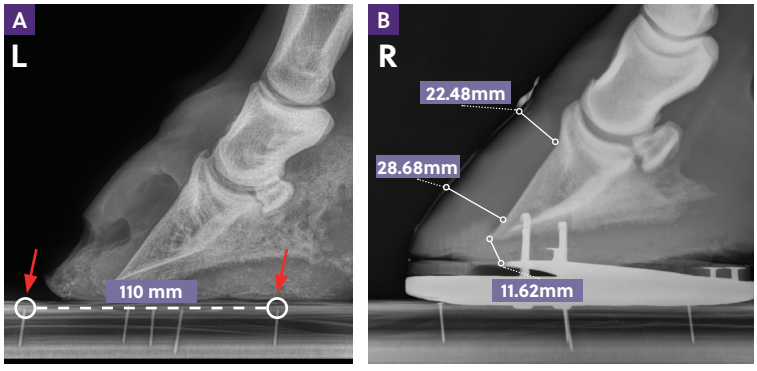

Figure 5. a) An example of image calibration to allow for more accurate measurement of the structures of the foot. The nails have been placed in the block at a set distance from each other (110 mm). b) Using the calibrated measurements to evaluate sole depth at the toe (11.62 mm), dorsal hoof wall/lamellae at the coronary band (22.48 mm) and dorsal hoof wall/lamellae at the toe (28.68 mm). This horse has rotation of the third phalanx with respect to the dorsal hoof wall.

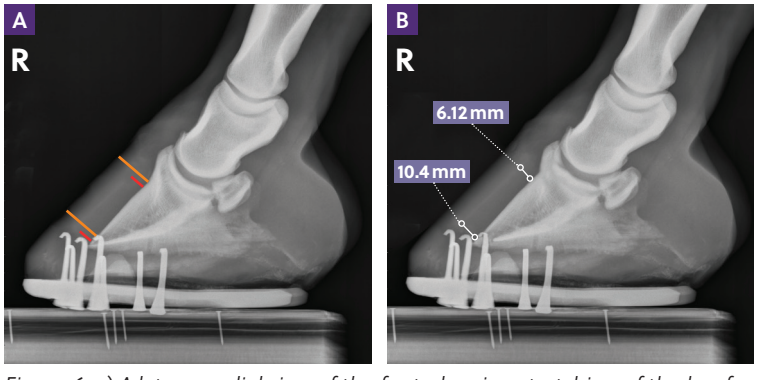

Figure 6. a) A lateromedial view of the foot, showing stretching of the hoof–lamellar interface without rotation of the third phalanx. The orange lines at the toe and just distal to the coronary band highlight the distance between the third phalanx and the hoof wall. The red lines highlight the hoof–lamellar interface. The orange lines are the same length top and bottom, while the red line is wider at the bottom, indicating stretching of the hoof-lamellar interface. b) An example of a horse with early laminitis in which there is minimal rotation of the third phalanx with respect to the dorsal hoof wall, but significant stretching of the hoof–lamellar interface at the toe (10.4 mm) compared to the measurement at the coronary band (6.12 mm).

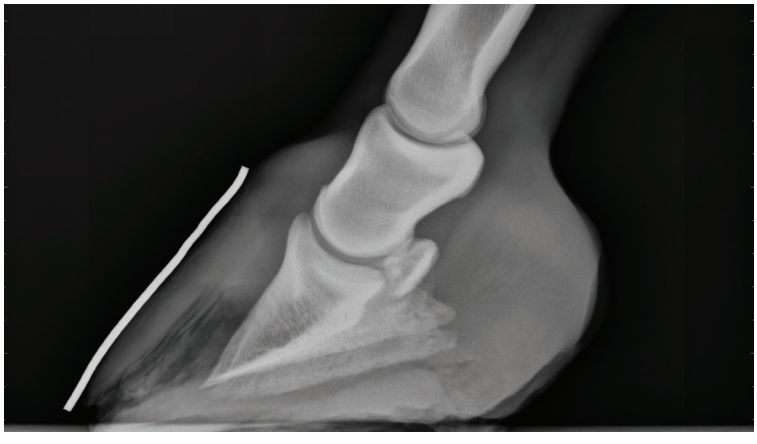

Figure 7. A lateromedial view of a laminitic foot demonstrating rotation of the third phalanx with respect to the dorsal hoof wall and gas tracking up the dorsal hoof lamellae (asterisk). Note the wire taped onto the dorsal hoof wall as a marker.

same one each time for consistency) or weigh the animal, and evaluate the cresty neck score. The cresty neck score is a better predictor of insulin dysregulation than body condition score, and ponies with a cresty neck score of ≥3 were five times more likely to have insulin dysregulation than those without (Fitzgerald et al, 2019).

Evaluation of resting insulin and adrenocorticotrophic hormone levels (or dynamic testing) in acutely laminitic horses is challenging and controversial because stress and pain (both of which are present in a laminitic horse) cause an increase in both values. The author does not usually test during acute episodes and instead initially treats endocrinopathies based on clinical suspicion (starting an overweight laminitic horse on thyroxine, and a hirsute laminitic horse on pergolide). The author prefers to test after the initial pain has subsided, so levels are more representative of the horse's true endocrine situation. It is critical to use the same laboratory for repeated analysis because methods for the quantitative analysis of insulin and adrenocorticotrophic differ, and reference ranges vary, making comparison difficult – if not impossible – between results from different laboratories (Go et al, 2023).

Treatment

One of the most critical features to remember about laminitis is that significant lamellar injury has occurred (during the developmental phase) by the time clinical signs are seen in the acute phase. As such, veterinarians are left 'playing catchup' and may not be able to overcome the cascade of events that has been initiated. This is particularly relevant in hyperinsulinaemia-associated laminitis, when there has often been chronic subclinical laminitis.

There are three mainstays of treatment for any case of laminitis:

1. Address the underlying cause
2. Provide anti-inflammatory and analgesic therapies
3. Biomechanically support the hoof.

Address the underlying cause: treat insulin dysregulation

Once insulin dysregulation has been definitively diagnosed or – if a definitive diagnosis is not possible – there is high clinical suspicion, the primary goal is to decrease insulin concentrations and improve tissue insulin sensitivity to decrease the ongoing initiating factor to the feet. The severity of an episode of laminitis is correlated with serum insulin concentrations in horses with pituitary pars intermedia dysfunction (Tadros et al, 2019).

Ideally, the majority of cases of insulin dysregulation would be managed with diet and exercise alone (although this is easier said than done in many cases). However, in some cases medical intervention is necessary, including: acute laminitis episodes (where insulin levels need to be rapidly decreased and the horse cannot be exercised), horses in which managing diet and exercise has not been successful over 3–6 months or horses with extremely high resting insulin levels or severe insulin dysregulation.

The primary pharmaceutical options used in practice in the UK to address insulin dysregulation include thyroxine, metformin and sodium-glucose cotransporter-2 inhibitors such as ertugliflozin ***(Appendix 1; available at: https://doi.org/10.12968/ukve.2024.8.1.14)***. Thyroxine has been the most used histori-

Table 2. Radiographic parameters associated with laminitis

Parameter	Laminitic horse	Normal horse
Dorsal hoof wall thickness* (*Figure 5b*)	>17 mm	<17 mm in Thoroughbreds Varies with breed
Stretching of hoof–lamellar interface distally (*Figure 6*)¶	Larger measurement of hoof–lamellar interface distally compared to proximally	Should be the same width throughout the length of the dorsal hoof wall
Position of the third phalanx‖	Rotated distally with respect to the dorsal hoof wall	Parallel to the dorsal hoof wall
Sinking of the third phalanx, increased coronary extensor distance†	>14–19 mm	<14 mm
Radiolucency of dorsal hoof wall‡ (*Figure 7*)	Gas lucencies within dorsal hoof wall associated with lamellar destruction and/or abscessation	None
Decreased sole depth*§	<15 mm	> 15 mm, can be >11 mm in Thoroughbreds
Lamellar wedge development†	Concavity of dorsal hoof wall, significantly thickening of dorsal hoof wall distally	None
Bony changes to the third phalanx†	Remodelling to a 'ski-tip' or 'elf shoe' appearance (*Figure 8a*) or osteopenia (*Figure 8b*) of the dorsodistal tip of the third phalanx	None

*Linford et al, 1993; †Herthel and Hood, 1999; ‡Morgan et al, 1999; §Redden, 2003; ‖Sherlock and Parks, 2013; ¶author's experience

Table 3. Diagnosing endocrinopathies in practice

	Equine metabolic syndrome	Pituitary pars intermedia dysfunction
Horses with high probability (ie, extremely consistent clinical signs), or first-line testing	Resting (basal) insulin*‡ and glucose concentration (horse not fasted; avoid grain or high-sugar feed for 6 hours before)	• Resting adrenocorticotrophic hormone concentration (always also measure insulin concentration) • Best to test in the autumn‡
Horses with lower probability (ie, milder clinical signs), or horses that are negative on first-line testing	Fasting oral sugar test or oral glucose test (preferred tests)‡	• Thyrotropin-releasing hormone stimulation test (note: some researchers favour measuring at 30 minutes rather than the initially described 10 minutes because there is greater accuracy when repeated samples are required and higher risk of incorrect diagnosis at 9 or 11 minutes) (Thane et al, 2022) • Do not perform this test in the autumn‡
	Intravenous insulin tolerance test (more for tissue insulin sensitivity)	Consider a combined thyrotropin-releasing hormone stimulation and oral sugar test§

* Note: stable-side insulin measurement — such as the Wellness Ready Insulin Test (Wellness Ready Labs) — provides stable-side insulin measurement in 15 minutes with acceptable precision, excellent linearity, and good association with the radioimmunoassay (Berryhill et al, 2023). † Note: consider using the glycaemic pellet – DysChEq by Boehringer-Ingelheim Vetmedica GmbH, Ingelheim, Germany (de Laat et al, 2023; Warnken et al, 2023). ‡ Must take into account seasonal variations. There is conflicting evidence regarding seasonal variation in insulin concentrations, but may be higher in the winter months. Resting adrenocorticotrophic hormone levels are higher in the autumn so must use seasonally adjusted reference ranges. Seasonal reference ranges for the thyrotropin-releasing hormone stimulation test are still under research, so the test should not be performed between mid-July and mid-November in the northern hemisphere (or between mid-January and mid-May in the southern hemisphere). § Combined thyrotropin-releasing hormone stimulation test and oral sugar test is diagnostic and can be more convenient (Hodge et al, 2019).

cally, and improves insulin sensitivity and promotes weight loss (Frank et al, 2008; Tóth et al, 2010). Metformin likely works at the level of the gastrointestinal tract to decrease glucose absorption and safely reduce glycaemic and insulinaemic responses in horses (Rendle et al, 2013).

The sodium-glucose cotransporter-2 inhibitors reduce renal glucose reabsorption and promote glucosuria, resulting in lowered blood glucose levels and, thus, insulin concentrations. Their use may begin to replace previous medications used to improve insulin sensitivity in horses. One study demonstrated that velagliflozin safely improved post-prandial insulin concentrations (Meier et al, 2019b) and prevented high-glucose dietary induction of Obel grade 1 or 2 laminitis in ponies (Meier et al, 2018a). Similarly, horses with insulin dysregulation treated with

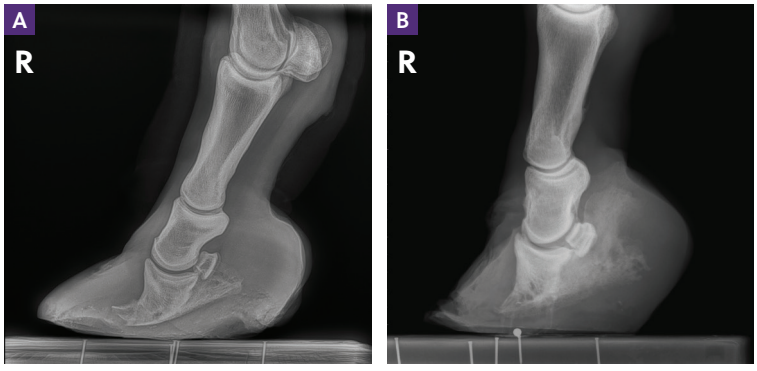

Figure 8. a) A lateral radiograph of a foot with chronic laminitis demonstrating remodeling (a 'ski tip' appearance, arrow) of the dorsodistal tip of the third phalanx, consistent with chronic laminitis. Note this horse also has a very long toe (asterisk) in need of a trim. b) A lateral radiograph of a foot with chronic laminitis demonstrating osteopenia (circled) of the dorsodistal tip of the third phalanx, consistent with chronic laminitis.

ertugliflozin for 30 days showed significant and long-term improvement in modified Obel laminitis score (Sundra et al, 2022). Evaluation of 10 horses with insulin resistance refractory to diet changes, thyroxine and metformin (with pergolide in pituitary pars intermedia disfunction-positive cases) showed that canagliflozin treatment was effective in substantially decreasing insulin levels, decreasing excess adipose deposits and improving laminitis pain (Kellon and Gustafson, 2022).

Dietary changes are almost always necessary in the laminitic horse as a result of overt obesity, insulin dysregulation or changes in daily needs because of decreased exercise associated with the laminitic episode ***(Appendix 2; available at: https://doi.org/10.12968/ukve.2024.8.1.14).*** In the UK, 21–62% of horses are obese (Harker et al, 2011) and, aside from increased risk of hyperinsulinaemia-associated laminits, obesity is linked to decreased survival rate in horses with laminitis (Menzies-Gow et al, 2010). Horses with insulin dysregulation have disproportionate insulin responses to eating even small amounts of moderate non-structural carbohydrate feedstuffs, and work in ponies with insulin dysregulation suggested that one of the most useful predictors of the risk of laminitis in this cohort is the insulin response to oral sugars (Meier et al, 2018b; Macon et al, 2022).

It is crucial to have the owner's agreement before embarking on dietary management. After estimating body condition score, weight and taking baseline photos as described in the workup, determine the horse's target body condition score and weight. Weigh the horse's current feeds and help the owner determine how much each scoop or section of each feed or hay weighs. Discuss the 'unhealthy' nature of obese adipose tissue (in particular what cannot be seen, such as visceral and retroperitoneal adipose tissue) and the negative effects it has on the rest of the body with the client, especially as relates to causing or potentiating whole body insulin dysregulation (Reynolds et al, 2019).

Although exercise is a safe and inexpensive way to improve insulin sensitivity and promote weight loss (when a horse's feet are stable enough and other comorbidities do not prevent it), this is rarely relevant in cases of active laminitis so is not discussed further here.

Anti-inflammatories and analgesics

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs ***(Appendix 3; available at: https://doi.org/10.12968/ukve.2024.8.1.14)*** remain the most common and universally available and accepted treatment for laminitis. Compared with other types of laminitis, there is less inflammation with hyperinsulinaemia-associated laminitis, but there is some, and non-steroidal anti-inflammatory drugs provide a good combination of anti-inflammatory and analgesic effects. Phenylbutazone and flunixin meglumine are readily available and are adequate in many cases. However, they are non-selective cyclo-oxygenase inhibitors that can be nephrotoxic and/or cause gastrointestinal ulceration in an idiosyncratic manner or with higher doses given for longer periods of time (most studies evaluated over 10 or 14 days) (Collins and Tyler, 1985; MacAllister et al, 1993).

Partially for that reason, the use of cyclo-oxygenase-1-sparing non-steroidal anti-inflammatory drugs has increased but these are not risk-free (Kivett et al, 2014; Bishop et al, 2023) and some clinicians (the author included) feel that they may not provide enough analgesia for acute cases. Reported comparisons for use in other types of orthopaedic (Jacobs et al, 2022) or visceral (Citarella et al, 2023) pain are difficult to extrapolate to laminitis pain. They may have a more useful role in specifically treating chronic laminitis, at which stage cyclo-oxygenase-2 has been shown to be increased, while the degree of pain has theoretically decreased (Watts et al, 2019).

Paracetamol

Paracetamol has comparable analgesic properties to a non-steroidal anti-inflammatory drug, but it works through an unclear mechanism of action involving cyclo-oxygenase inhibition and serotonergic activity, with weak anti-prostaglandin activity. Recent evaluation showed that paracetamol provides analgesia similar to phenylbutazone, with a wider margin of safety (Mercer et al, 2023). It may well be worth considering as an adjunct to non-selective non-steroidal anti-inflammatory drugs, or in lieu of them in cases that cannot tolerate them.

Cryotherapy

Continuous distal limb cryotherapy can prevent the development of sepsis-associated laminitis, but intermittent cryotherapy also has both analgesic and anti-inflammatory effects and is appropriate for hyperinsulinaemia-associated laminitis (Cassimeris et al, 2021). Options for administration include standing the affected limb(s) in a bucket of ice water (with the horse cross-tied or held) for 20–120 minutes as many times daily as is possible (*Figure 9*); placing the affected limb(s) in a commercial immersive cold water boot (with or without compression), or bandaging/taping used 5 litre fluid bags filled with ice slurry around the hooves ***(Appendix 4; available at: https://doi.org/10.12968/ukve.2024.8.1.14).*** There are minimal side effects aside from possible mild dermatitis of the coronary band/distal limb, and the method chosen likely will reflect the available resources and the horse's size and compliance (van Eps and Orsini, 2016).

Gabapentin

Gabapentin is a gamma-aminobutyric acid neurotransmitter inhibitor analogue with analgesic properties. Historically, it was reserved for chronic, severe cases, but more recently experts have advocated

instituting therapy at the first signs of pain to help prevent the 'wind-up' phenomenon and central sensitisation (ie hyperalgesia and allodynia) associated with laminitis. A higher dose than previously used is necessary and safe (Gold et al, 2022).

Other analgesic options

Horses in extreme pain will benefit from multimodal analgesia. This degree of pain is less common with hyperinsulinaemia-associated laminitis than with other causes of laminitis, so the reader is referred to alternate resources for more details (Hopster and van Eps, 2019). Multimodal analgesia may include opioids (morphine, buprenorphine, butorphanol or tramadol (given orally), keeping in mind the risks of intestinal ileus and the intricacies of administering controlled medications), α-2 adrenergic receptor agonists, ketamine or lidocaine. Analgesia may be given intermittently, as a constant rate infusion or via epidural catheter.

Hoof support

It is critical to apply some type of hoof support to active laminitis cases as soon as possible. The primary goal is to shift the weight-bearing from tissue with load-induced vascular compromise to healthier areas, thus decreasing pain and allowing healing (O'Grady and Parks, 2008; Bras and Morrison, 2021). Most often, this involves moving weight-bearing to the frog and heel bulbs to shift weight off the toe area – this is most commonly affected by laminitis. This plan may vary in severe cases with diffuse lamellar damage (also known as 'sinkers') or those with unique presentations.

The deep digital flexor tendon exerts a large force on the third phalanx. Reducing this tension in laminitic cases decreases the shearing forces on the abnormal and weakened lamellae and the resultant compression of the sole that damages the corium and blood vessels (Bras and Morrison, 2021). Three common ways to decrease the tension from the deep digital flexor tendon include raising the heel, decreasing breakover (by trimming to shorten the toe – use radiographs to guide this), and rocker shoes or boots. Tenotomy of the deep digital flexor tendon is used by some veterinarians in acute cases, while others reserve it for chronic cases; this choice depends on the veterinarian's familiarity with the procedure and previous outcomes with the technique.

A principal issue in shod horses is whether or not to remove the shoes the horse is currently wearing. If this can be done atraumatically, it should be as it creates the opportunity to provide better foot support (O'Grady and Parks, 2008). However, if the horse is very sore, the farrier is not available and atraumatic or rapid removal is not possible or the horse has very poor-quality hooves, then the author often leaves the current shoes for the first several days and places a commercial boot with a pad or tapes on styrofoam over the shoe. It is critical that the client check (several times a day) that these have not slipped out of place, putting more pressure on the wrong areas. The author feels that supporting the sole, minimising the horse's movement, and keeping the horse deeply bedded is more critical than the 'proper' foot support in the acute phase.

Once the foot has stabilised and comfort level has improved, then the veterinarian can work with the farrier to pull the shoes, trim the hoof and place the next stage of foot support (Curtis et al, 1999; Bras and Morrison, 2021). In some cases, distal limb anaesthesia via abaxial nerve blocks with lidocaine or mepivicaine is necessary to facilitate farrier work. In those instances, do not allow the horse to walk freely until the nerve blocks have worn off; doing so may lead to grave lamellar damage. It is also critical to ensure the horse has non-steroidal anti-inflammatory drugs (or another analgesic) on board before farriery, as it is likely to increase soreness, at least briefly, as a result of the unavoidable forces applied to the hoof wall and laminae during this procedure.

Figure 9. Cryotherapy options – the front feet are in an ice water slurry in a bucket (with the horse cross-tied); note that the water level should ideally be higher up to the level of the mid-metacarpal region. The hind feet are in used intravenous fluid bags (filled with ice slurry) that have been taped onto the feet.

There are numerous commercially available and homemade options for providing hoof support to the laminitic horse ***(Appendix 5; available at: https://doi.org/10.12968/ukve.2024.8.1.14).*** The majority of these aim to elevate the heel, move weight-bearing to the frog, heel bulbs or sole, take the weight off the toe where it is painful and crushing the circumflex marginal blood vessels and to move the breakover point palmarly/plantarly (O'Grady and Parks, 2008). Some horses with chronic hyperinsulinaemia-associated laminitis can be managed barefoot if they have good quality hooves and an experienced farrier.

Activity level

Confine a horse in the acute phase of laminitis to a deep, softly bedded (or sand-filled) stall or paddock, with no exercise because the lamellae are unstable and at risk of further injury (Bras and Morrison, 2021) ***(Appendix 6; available at: https://doi.org/10.12968/ukve.2024.8.1.14).*** A good rule of thumb is 1 week of confinement per day of acute lameness (Hopster and van Eps, 2019).

Make sure the client pays close attention to the horse's appetite and faecal output during confinement because there is an increased

Table 4. Prognosis

	Mild acute	Moderate acute	Severe acute
Degree of lameness	Mild (<modified Obel grade 4)	Moderate (<modified Obel grade 8)	Severe (>modified Obel grade 9)
Radiographic changes	None	Mild	Severe
Time to resolution of lameness	Within days	Weeks	Months, if ever
Long-term prognosis	• Gradual return to work in weeks • Lifelong attention to risk factors	• Possible return to work in months • Lifelong hoof management	• Athletic career most likely over (Cripps and Eustace, 1999; Sherlock and Parks, 2013) • Possible euthanasia
Note: any of these can be superimposed over subclinical or chronic disease			

risk of gastric ulcers and colic, particularly large colon (Hillyer at al, 2002) or caecal impaction (Campbell et al, 1984). Once the third phalanx is stable within the hoof wall (as determined by comfort level and repeated radiographs) and is properly mechanically supported, the horse may be allowed restricted turnout on a woodchip or sand area (avoid grass because of its glycaemic nature) to move around at their own will (as long as they are not likely to be very active on their own). This could be after 1–2 weeks (in an acute episode) or after months (in chronic active cases).

Provided the horse remains comfortable (and the foot remains stable both radiographically and clinically to the farrier and veterinarian) with that amount of movement, the horse can start with 5 minutes of hand-walking a day, increasing this by 5 minutes every 4–5 days until reaching 30 minutes/day at least 5 days a week. This may be undertaken more quickly in horses with an acute episode of laminitis without any radiograph changes. In horses with chronic laminitis, this process may take almost a year because it takes 8–10 months to grow out new hoof (Bras and Morrison, 2021).

If the horse remains comfortable with this regimen, the veterinarian can consider putting a rider on the horse and walking under saddle. Slow return to work, as long as the horse shows no signs of regression, can be undertaken similar to any other situation in which a horse has been out of work and is starting to return to full work.

Prognosis and follow up

While the short-term prognosis for life with hyperinsulinaemia-associated laminitis is better than for systemic inflammatory response syndrome-associated laminitis (*Table 4*), the high recurrence rate makes the long-term prognosis for soundness and life guarded. Recurrence is, in part, because of a failure to appropriately mitigate the risk factors, but is more driven by chronic weakness of the lamellar tissues (Karikoski et al, 2015) and development of the lamellar wedge (Herthel and Hood, 1999). A retrospective study looked at 37 horses with hyperinsulinaemia-associated laminitis across 16 clinics in Germany, and showed that two-thirds of the horses improved markedly within 2 weeks, but about one-quarter took longer than 2 weeks (interestingly, these were significantly younger) or had a relapse (Sillence et al, 2022).

The lamellar wedge develops between the third phalanx and the hoof wall in response to stretching and mechanical failure seen in lamellar tissue with hyperinsulinaemia-associated laminitis (*Figure 10*). Its development is generally irreversible and presents a challenge for the foot recovering from hyperinsulinaemia-associated laminitis. It makes it difficult to realign the foot and stabilise the suspensory apparatus of the hoof without pain (Collins et al, 2010).

In the long term, horses with hyperinsulinaemia-associated laminitis are prone to sub-solar hoof abscesses. It can be disheartening when a horse that was doing well is suddenly significantly more lame, so it is important to warn clients that these are likely. Management is similar as to other hoof abscesses, except they can be more persistent and extensive in their damage because of the nature of the underlying lamellar damage.

A Danish study highlighted the critical nature of hyperinsulinaemia-associated laminitis when they reported that one-third of horses with the condition are euthanised within 1 year (Luthersson et al, 2017) and one-third of horses with hyperinsulinaemia-associated laminitis have a recurrence within 2 years (de Laat et al, 2019). Reported recurrence rates for hyperinsulinaemia-associated laminitis are 34% (de Laat et al, 2019), while reported recurrence rates for laminitis seen at first-opinion practice in the UK were reportedly 72% (Welsh et al, 2017). The risk of recurrence has been directly linked to resting fasting insulin levels (de Laat et al, 2019; Menzies-Gow et al, 2017; Knowles et al, 2023), and hyperinsulinaemia is 90% sensitive and specific for non-survival as a result of laminitis within 2 years in horses with pituitary pars intermedia dysfunction (McGowan et al, 2004).

A veterinarian treating a laminitic horse should in frequent contact with the client, caregiver and farrier. Use objective measurements and keep good records from each visit in order to make monitoring more reliable; these cases can go on for months or years, and the timeline and history can get blurry. Take photos of the horse's body condition and feet at each visit, repeat radiographs and laboratory work on a schedule that takes into account the horse's condition as well as the client's financial situation and be direct with clients from the start about prognosis based on existing experience and expertise. It can be a balancing act to manage expectations – ensuring clients know this needs to be a team effort, and that their complete commitment is necessary – without 'scaring them away' from pursuing treatment yet still providing an optimistic (when possible) and realistic prognosis.

Prevention

If veterinarians are aware of the risk factors for, and signs of, subclinical or clinical episodes of hyperinsulinaemia-associated laminitis and educate their clients, this disease is largely preventable in most horses. These risk factors include:

- Documented insulin dysregulation

- Regional or generalised adiposity
- Abnormal hoof growth
- Documented or suspected pituitary pars intermedia dysfunction
- A history of sore feet (especially after farriery or when put on lush pasture)
- Historical laminitis
- Stretching or bruising of the white line (typically noted by the farrier).

Annual evaluation (eg, at the time of vaccinations or dental work) in horses with any of these signs or risk factors should include:

- Body condition score or weight analysis
- Measurement of cresty neck score
- Evaluation of regional adiposity, hair coat, hoof quality and hoof growth
- If possible, baseline foot radiographs.

Furthermore, at least annual (perhaps seasonal) screening should be recommended for horses with any of the clinical signs listed above, including evaluation of insulin status and (in horses over 15 years old with clinical signs), testing for pituitary pars intermedia dysfunction.

It is becoming easier to test for endocrinopathies in the field in order to improve client compliance. For example, combined thyrotropin-releasing hormone stimulation test and two-step insulin sensitivity testing yields satisfactory results (Horn and Bertin, 2019). A large body of work has focused on determining the best way to evaluate insulin sensitivity in the field as it is so closely associated with risk of hyperinsulinaemia-associated laminitis. The oral sugar test is considered the most sensitive and readily available option for field practitioners across seasons (van den Wollenberg et al, 2020; Macon et al, 2022). Ideally, veterinarians should consider re-evaluating negative horses over different seasons to avoid missing a diagnosis (Macon et al, 2022). That said, retesting positive horses across seasons to assess response to therapy can be challenging because of individual variation throughout the year. Thus, is it important to use a combination of clinical condition and laboratory values to guide therapeutic and management recommendations.

Corticosteroid administration (Potter et al, 2019), seasonal lush pasture access, stressful events and hospitalisations might exacerbate insulin dysregulation and lead to clinical episodes of hyperinsulinaemia-associated laminitis in horses that are predisposed to insulin dysregulation. Either repeated or an extended duration of sedation with α-2-adrenoceptor agonist, especially xylazine (Kritchevsky et al, 2020) can predispose some horses to prolonged hyperinsulinaemia, thus increasing the risk of laminitis (Box et al, 2021). Even horses without previously identified risk factors can develop insulin dysregulation when administered corticosteroids (Timko et al, 2022), so it is possible that stressful situations that cause endogenous cortisol increases can also cause clinically significant insulin dysregulation and a risk of hyperinsulinaemia-associated laminitis.

Numerous nutritional supplements are available to help prevent insulin dysregulation and/or hyperinsulinaemia-associated laminitis, only a few of which have been evaluated. Some may contain high levels of sugar to improve palatability so it is important to check the nutritional content and/or measure the horse's insulin levels after ingestion if there is any doubt. Products containing resveratrol and synergistic polyphenol and amino acid blend including leucine (which may alter the microbiome thereby improving lipid metabolism) led to lower post-oral sugar test insulin levels, weight loss and higher high molecular weight adiponectin levels in 15 horses with equine metabolic syndrome compared to horses not on the supplement. This suggests that a similar supplement may improve some clinical manifestations of equine metabolic syndrome and insulin dysregulation, thus decreasing the risk of hyperinsulinaemia-associated laminitis (Manfredi et al, 2020). Supplements that contain chromium and magnesium are commonly suggested for management of insulin dysregulation, extrapolated from human medicine. The study that evaluated them did not report any changes in resting insulin levels, insulin sensitivity (assessed by insulin-modified frequently sampled intravenous glucose tolerance tests), or morphometric measurements in laminitic obese horses fed the supplement (Chameroy et al, 2011). Horses should receive the recommended daily amounts of magnesium and chromium, but the effect of supra-physiological amounts of these minerals on insulin dysregulation has yet to be elucidated.

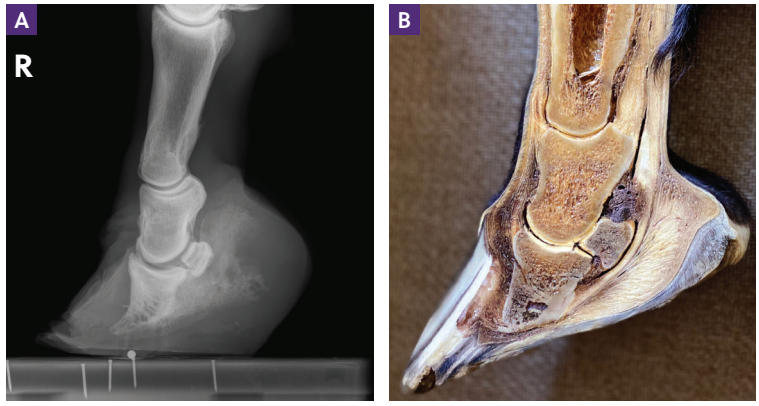

Figure 10. a) A lateral radiograph of a foot with chronic laminitis – the yellow dashed line highlights the lamellar wedge. b) A post-mortem preserved specimen of a foot with chronic laminitis – the yellow dashed line highlights the lamellar wedge.

A strong working relationship with a trusted farrier is crucial, both for the veterinarian and the client. The farrier is often the first member of the horse's care team to identify a hoof issue before clinical signs are evident to the client.

Future directions

Various pathways involved in hyperinsulinaemia-associated laminitis are being studied to better understand the pathophysiology and thus develop novel possible therapeutics. These include:

- Clinically applicable inhibitors of insulin-like growth factor 1 receptor, mechanistic target of rapamycin complex 1, mitogen-activated protein kinase, signal transducer and activator of transcription proteins, heat shock protein-90 and proinflammatory cytokines
- Acute phase proteins in adipose tissue and skeletal muscle
- Analogues of incretin hormones of the enteroinsular axis that affect insulin dynamics
- Analgesic options such as soluble epoxide hydrolase inhibitors.

KEY POINTS

- Hyperinsulinaemia-associated laminitis is the most common type of laminitis encountered in equine practice.
- Strict focus on mitigating the risk factors, and early recognition and diagnosis of insulin dysregulation greatly decreases the risk of hyperinsulinaemia-associated laminitis.
- Early treatment and a committed client, veterinary and farrier team is critical to improve the prognosis.
- Treatment of hyperinsulinaemia-associated laminitis should encompass a three-pronged approach: treat the underlying cause; provide anti-inflammatory and analgesics drugs; and biomechanically support the foot.
- The field of equine endocrinopathic disease is very active so it is important to stay up to date on potential diagnostics and therapeutics.

There is a lot of work going on, so there is great potential for future developments in the diagnosis and treatment of equine endocrinopathies and hyperinsulinaemia-associated laminitis.

Conclusions

Hyperinsulinaemia-associated laminitis is the most common form of laminitis encountered in equine practice, and it can generally be prevented if owners are aware of the risk factors, and possible episodes are caught and treated early. A patient's prognosis can vary, and a wide range of therapies including a number of medications (anti-inflammatory and analgesic), cryotherapy and hoof support are used in conjunction with addressing the underlying insulin dysregulation. There is ongoing research around hyperinsulinaemia-associated laminitis, so veterinarians should ensure they are up to date on diagnostic methods and therapeutic options for horses with the condition. EQ

Conflicts of interest

The author declares that there are no conflicts of interest.

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