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This paper was written when I was in veterinary school. I am posting it on the website because many of my clients with Cushing's or Metabolic Syndrome horses are interested in following research on this topic. The paper addresses the question "what are the effects of excess glucocorticoids on hoof health?" This is primarily a literature review on the topic of endocrine associated laminitis, and includes speculation on one of my research interests—subclinical laminitis.

Mechanisms of Equine Endocrinopathic Laminitis

Introduction

Laminitis is an equine foot disease characterized by dysfunction of the tissues that secure the distal phalanx to the wall inside the hoof capsule. Laminitis is commonly studied using experimental models that induce acute laminar pathology. In experimental models, acute laminitis is induced by carbohydrate overload or toxin administration. While toxicity and severe carbohydrate overload do cause acute severe laminitis, the most common form of laminitis observed by equine clinicians is a slow-onset chronic laminitis. The standard clinical presentation is rarely due to toxins. There appears to be a link to carbohydrate metabolism, but naturally occurring peracute or acute cases are rare.

Histological lesions of the inner hoof wall include morphological changes at the dermal epidermal junction in both acute and chronic laminitis. Macroscopic lesions do not appear in the outer hoof wall in experimentally induced laminitis, presumably because changes to basal keratinocytes take weeks or months to be reflected in altered horn growth that can be seen grossly. Although research using carbohydrate models continues to elucidate causative mechanisms and pathway, an alternative research direction may offer explanations for the common clinical picture of slow onset chronic laminitis: endocrinopathy associated laminitis. There is not presently an experimental model for endocrinopathic laminitis. But a growing body of research, in both the equine and human medical fields, begins to explain possible mechanisms of subclinical and chronic laminitis.

Endocrine associated laminitis has been linked to insulin resistance, Cushing's disease, and stress.[1] A commonality in all endocrine associated laminitis research is that glucocorticoids (GCs) are believed to play an important role. Glucocorticoids are a group of steroid compounds that have anti-inflammatory and metabolic effects. They are produced by the adrenal cortex during times of stress. There are also exogenous forms of glucocorticoid, including popular drugs in equine practice such as dexamethasone and triamcinolone, used for a wide range of conditions. A review of possible endocrinopathic mechanisms of laminar degeneration may add clinical relevance to our current knowledge derived from experimental models of laminitis. Proposed mechanisms of endocrinopathic laminitis may be tested in future research, and may ultimately provide equine practitioners with valuable tools for preventing, treating, and managing this disease.

Can glucocorticoids cause laminitis in horses? Many horse owners and equine practitioners strongly believe the answer is yes. However scientific evidence for a direct association is lacking.[2] There are several well-established experimental models for laminitis induction: steroid administration is not one of them. Despite anecdotal evidence of horses developing laminitis after exogenous steroid use, attempts to induce laminitis with high dose steroids have not been reproducible. One report presented a retrospective uncontrolled study of the clinical use of triamcinolone in horses.[3] Of 205 cases studied, 3 horses had laminitis associated with the steroid therapy; but these 3 horses had been previously treated for laminitis. Of the 202 horses without prior incidence of laminitis, none developed laminitis after being treated with triamcinolone for musculoskeletal disorders.

Exogenous steroids are routinely used in equine practice for a wide variety of equine inflammatory disorder including heaves, degenerative joint disease, osteochondrosis, allergies, vaccine reactions, and various incidences of soft tissue swelling.[4] Dose-titration studies of glucocorticoid use in horses have not been done, and concerns about possible side effects of laminitis often limit the use and/or dose of steroids administered.[2] On the other hand anecodotal evidence from equine clinicians suggests that higher than currently recommended doses can be safely given to the majority of horses.

Background: gastrointestinal disease and laminitis pathophysiology

Gastrointestinal dysfunctions in horses have long been associated with laminitis. Two competing theories on laminitis pathogenesis are in agreement on one major point: events within the intestine trigger alterations in the digital laminae. One theory suggests that hemodynamic changes following gastrointestinal disease result in hypoperfusion to the foot, followed by reperfusion injury to the laminae.[5] Another theory suggests that gastrointestinal disease results in exotoxin release into systemic circulation which results in derangement of matrix metalloproteinases within the foot, leading to laminar injury.[6]

The relevance to GC-induced laminitis may arise as an indirect effect whereby GCs increase intestinal permeability. Studies in rats have shown that stress-induced endogenous GCs as well as exogenous GC and non-steroidal anti-inflammatory drugs reduce gastrointestinal barrier function.[7] A similar effect may also be present in the horse. Altered intestinal permeability may permit the absorption of toxins and proinflammatory agents into the systemic circulation. These “trigger factors” may eventually reach the digital vessels, causing direct and indirect effects of laminitis within the foot. Research has shown that although endotoxin administration does not directly cause laminitis, it does result in digital hypoperfusion by inhibiting nitric oxide pathways.[8] Research comparing laminitis prone ponies to healthy ponies found increased concentrations of amines in cecal contents and plasma of those with a history of laminitis.[9] Amines detected had vasoconstrictive properties, believed to mimic effect of endogenous amines such as epinephrine, norepinephrine, and dopamine. Exotoxins have been shown to directly induce laminitis in equine hoof explants by upregulating matrix metalloproteinase activity in laminar tissue basement membrane.[10] However serum markers of lamellar basement membrane degradation have not been detected in peripheral plasma.[10]

If GCs act at the level of the gastrointestinal tract in contributing to laminitis, then perhaps regional limb perfusion of GCs may act to reduce laminar inflammation without causing a secondary counteracting effect. Yet there is only one report in the literature, from 1965, supporting local GC therapy for laminitis.[11] More recent research suggests that GCs may act locally as well as systemically in contributing to laminar pathology.[12] Mechanisms of GC action have been implicated in many proposed theories of laminitis pathogenesis.[13] Due to the

difficulty of studying naturally occurring chronic laminitis in live horses, research has focused on acute experimentally induced laminitis. Despite the limitations of generalizing from these experiments to the clinical picture of chronic laminitis, plausible inferences can be made. Recent advances in biopsy techniques in live horses suggests that future research may focus more on naturally occurring laminitis.[14] Endocrinopathic laminitis is likely to become an important research topic.

The paradox of glucocorticoids

Inflammation is the vascularized tissue response to injury, and promotes healing by multiple mechanisms. Inflammation entails a complex series of events involving changes in hemodynamics, vessel permeability, and leukocytic activation. Detailed mechanisms of these major inflammatory changes have been reported in laminitis research literature. A partial list of documented factors present during laminitis episodes includes pro-inflammatory cytokines,[15] lipopolysaccharide,[16] COX-2 enzymes,[17] matrix metalloproteinases,[10] and platelet-neutrophil aggregates.[18] Since laminitis is associated with multiple inflammatory events, and GCs are known to have potent anti-inflammatory effects on numerous equine conditions, why wouldn't they be a perfect therapy for laminitis? Furthermore, if endogenous GC production is the body's natural anti-inflammatory, why wouldn't stressed and/or Cushing's horses, with abundant cortisol secretion, be resistant, rather than prone, to laminitis? It seems counter-intuitive that GCs do not work to reduce laminar inflammation. It is additionally puzzling that GCs may even act to stimulate or perpetuate laminar pathology. A review of physiologic GC effects, and investigation of GC effects in the equine foot reveals possible explanations for this apparent paradox.

Glucocorticoid physiology

Cortisol is the physiologic glucocorticoid in horses, one of the steroid hormones produced and secreted by the adrenal cortex. Cortisol secretion rises in response to stress, which can include diverse events such as pain, temperature changes, trauma, illness, training, showing, trailering, feeding high concentrate rations, or keeping horses in stall confinement. Cortisol release in the face of stress is a physiologic response. Glucocorticoid receptors exist in almost all cells so that a cortisol-mediated stress response will enhance survival when an animal is challenged by trauma, infection, or any other threat. A key role of GCs in a stressful situation is to maintain positive energy balance by supplying adequate glucose to critical tissues and organs. Cortisol release induces hyperglycemia for immediate energy needs to the brain. Cortisol also functions to down-regulate inflammatory pathways.

Part of the explanation for the role of GCs in laminitis may lie in the distinction between physiologic short-term GC release (or exogenous administration) versus protracted GC excess during chronic conditions. Exogenous GCs do not reliably cause laminitis in normal horses administered high doses over short periods of time. However no attempts have been made to set up a longitudinal experimental model whereby even "physiologic" doses are given repeatedly over the long term. It is not known whether endogenous and exogenous steroids exert the same effects on laminar tissue. Based on the widely observed link between high endogenous cortisol in Cushing's associated laminitis, and anedoctal reports of exogenous GCs causing chronic laminitis, it is assumed that the actions are similar.

To understand the pathologic consequences of GC excess it helps to begin with the role of GCs in a horse's "natural" environment. In nature, horses live outdoors in small herds, grazing most of the time, with short bursts of activity in response to growth and survival needs (obtaining food, escaping from predators, socializing). Activation of the stress-response upregulates the hypothalamic-pituitary-adrenal (HPA) axis resulting in elevated circulating

cortisol. In nature, a horse with foot pain severe enough to restrict its movement is not likely to survive. In domestication, much of what people do with horses entails activation of the equine stress response, upregulation of the HPA axis, and in the case of laminitis, prolonged pain with restricted movement.

There is no clear demarcation between physiologic short-term GC elevation and the pathologic long-term stimulation. Still, the basic idea remains plausible: GC excess may paradoxically cause or perpetuate the very conditions it is used to treat. Glucocorticoid release has systemic and local effects that may play a role in laminitis. Protein catabolism causes multiple abnormal biochemical processes that may affect the equine foot: skin atrophy, poor wound healing, connective tissue weakening, and bone resorption. The potential mechanisms of GC-induced laminitis involve several target tissues and endocrine mechanisms including laminar dermal-epidermal junction, vasculature, insulin/glucose metabolism, obesity-associated laminitis, Cushing's associated laminitis, and hypothyroid associated laminitis. A brief look at each of these mechanisms offers possible explanations for chronic GC induced hoof damage.

Glucocorticoid effects on hoof tissue

The equine hoof is integument and therefore subject to variants of cutaneous associated endocrine disorders commonly seen in other species. The laminar bond holding the distal phalanx to the hoof wall is a highly specialized dermal-epidermal junction. GC excess inhibits collagen synthesis and fibroblast growth which are part of the laminar junction's normal remodeling process.[19] Research has shown that weakening and eventual destruction of the laminar basement membrane is an important step in the pathogenesis of acute laminitis.[20] Abnormal matrix metalloproteinase (MMP) activity in laminar tissue has been experimentally induced with carbohydrate overload.[10] Glucocorticoids should theoretically down-regulate MMP activity, but there may be an unexpected effect that has yet to be clarified. The GC effect on hoof MMP activity is not known, but other processes of basement membrane integrity, such as maintaining the health of keratinocytes, are known to be inhibited by GCs.[20] Therefore even if GCs were shown to stabilize proteinase activity, the destructive effects of GCs on keratinocytes appears to take precedence in the pathogenesis of lamintis.

Basal keratinocyte attachment failure has been studied in experimentally induced laminitis.[19] Keratinocytes are rich in GC receptors. Research has documented that dexamethasone decreases anchoring proteins between the basement membrane and basal keratinocytes.[21] Experiments on bovine hoof have shown that cortisol directly inhibits keratinization.[22] Given the similarities between equine and bovine laminitis, it is likely that the same effects would be seen in equine hoof.

Glucocorticoid effects on blood vessels

Glucocorticoids act on vasculature both directly and indirectly. A direct effect of GCs is reduced tissue perfusion resulting from contraction of vascular smooth muscle. Research has demonstrated that intramuscular dexamethasone or triamcinolone administered to healthy horses daily for 4 to 7 days increase contractility in digital artery smooth muscle via inhibition of potassium channel activity.[21] Another experiment demonstrated that betamethasone and hydrocortisone potentiate catecholamines' (epinephrine, norepinephrine, and serotonin) vasoconstrictive effects on large digital vessels.[23] Effects of altered digital perfusion may play a role in predisposing laminar tissues to further insults.[23] Research on small vessel circulation is needed to more fully elucidate mechanisms of vascular changes in laminitis. An indirect effect of GCs on vasculature arises from insulin resistance.

Glucocorticoid effects on insulin and glucose metabolism

Glucocorticoids are known to interfere with insulin activity. Thus GCs have been implicated in insulin resistance, which is part of the clinical picture in Cushing's disease and equine metabolic syndrome.[24] Hyperglycemia is not always found with insulin resistant horses but it has been documented. Like hyperglycemic effects in diabetic human patients, elevated glucose in horses may exert a glucotoxic endotheliopathy in susceptible vasculature of the foot. Endothelin-1 and reduced nitric oxide release from endothelial cells has been documented in equine digital blood vessels.[25]

Another mechanism linking GCs, glucose, insulin, and laminitis is suggested by a study on triamcinolone metabolism in horses.[26] Triamcinolone given for 8 days at the upper limit of the recommended dose range showed prolonged periods of hyperglycemia and hyperinsulinemia with effects persisting for 3-4 days after drug therapy was discontinued. Investigators drew on evidence from a previous study on digital glucose metabolism to explain possible links to laminitis. Experiments demonstrated that in vitro laminitis was induced in explants kept in physiologic saline and deprived of glucose.[27] Additional tissue samples from the same feet kept in glucose medium retained normal laminar junction as seen on histology slides. In the triamcinolone study, researchers found no significant changes in plasma glucagon or serum non-esterified fatty acids, which suggests that hyperglycemia following exogenous steroid administration can be explained, at least in part, by reduced utilization of glucose. The long duration of triamcinolone action alters glucose metabolism, and this may play role in laminitis by reducing glucose uptake by laminar keratinocytes. Although no data exist on the metabolic rate or glucose requirements for equine hoof tissue, the keratinocytes are believed to have a high glucose requirement and may be uniquely susceptible to deprivation of glucose delivery and/or uptake.[27]

Glucocorticoids may have an indirect effect on laminar tissue via their modulation of glucose metabolism as explained above. An experiment on bovine hoof horn documented a direct effect on hoof explant tissue whereby hydrocortisone inhibited keratin protein synthesis.[28] Given the similarities between bovine and equine hoof horn, it is likely that a similar effect would occur in horse hoof protein synthesis. Whether demonstrated *in vitro* effects are reproducible *in vivo* may be investigated in future research.

Paracrine and autocrine mechanisms of GCs

Degenerative changes in hoof laminar tissues appear to be influenced by elevated circulating levels of GCs, as described above. But local control of cortisol metabolism may play an important role in modulating tissue-specific effects in laminitis. An experiment was conducted to test the hypothesis that changes in integumentary 11B-hydroxysteroid dehydrogenase-1 (11B-HSD-1) leads to elevated local tissue levels of GCs which contribute to laminitis development.[12] The bidirectional enzyme 11B-HSD-1 inactives or activates the conversion of cortisone to cortisol. This enzyme and related moieties (including 11-ketoreductase) act systemically and locally to maintain physiologic levels of tissue-specific GCs. The study found that skin and laminar tissues of laminitic horses had elevated levels of 11B-HSD-1 compared to levels measured in healthy control horses. Tissue activity was found to be highest in acute laminitis, followed by chronic laminitis, and lowest in the control horses. Authors of this paper noted that although tissue response to steroids is receptor-mediated, further control is exerted by autocrine or paracrine amplification by 11B-HSD-1.

Obesity associated laminitis

Obese horses with laminitis are frequently observed in equine practice. Associations between body condition score and laminitis are the subject of active research interest today. There is no direct link, as practitioners see that most obese horses are not laminitic. But of those that are both obese and laminitic, research is starting to show possible explanations. Possible endocrinopathies are now thought to explain obesity-associated laminitis. One hypothesis is that obesity-associated laminitis has a similar pathophysiology to the development of atherosclerosis in humans with type 2 diabetes: vascular changes and a hypercoagulable state in equids genetically predisposed to hyerpinsulinemia, dyslipidemia and hypertension.[24]

Research in lab animals and humans has documented mechanisms of adipocyte metabolism linking hormones such as leptin and resistin to metabolic syndrome.[29] Omental adipocytes have been found to be more metabolically active than was previously thought. Adipocytes are an important source of endocrine signaling that promote inflammation and decreased insulin sensitivity. This fat cell endocrinology may play a role in equine laminitis, as noted above in the discussion on tissue-specific effects of 11B-HSD-1. In addition to autocrine or paracrine effects within laminar tissue, GCs may affect systemic metabolism in certain horses. Obese, laminitic horses, often have abnormal fat deposition, with distinct "fat pads" in the supraorbital fossa, over the tail head, and in the crest of the neck. The authors of the tissue-specific cortisol research discussed above speculated that enhanced integumentary activity of 11B-HSD-1 may be analogous to endocrine-associated GC effects in human adipose tissue.[12]

Obese horses with chronic laminitis are often diagnosed as having metabolic syndrome, which can be supported by laboratory tests showing insulin resistance. In humans, the metabolic syndrome includes hypertension and dyslipidemia.[30] One study documented an association between laminitis and hypertension, finding fluid shifts, CBC changes, and serum glucose alterations occurred consistent with circulating GCs and/or catecholamines.[31] There has also been some research on laminitis and hyperlipidemia.[32] Hyperlipidemia is an important condition in obese ponies[33] and miniature horses.[34] Anorexia secondary to pain (often due to colic and/or laminitis) can alter energy metabolism leading to rapid mobilization of serum free fatty acids, hepatic lipidosis, and hepathoencephalopathy.

Pathologic shifts in energy metabolism can also during late pregnancy or lactation, which are periods of time that brood mares are known to be susceptible to laminitis. Other pregnancy induced changes that may affect laminar tissues include a state of relative immune suppression, hemodynamic changes, and effects of relaxin on connective tissues in the foot.

Current understanding of stress-induced results of negative energy balance would suggest that GC effects at least partially explain laminitis in horses with these metabolic changes. But there has been little clinical interest (as it is not practical) in measuring blood pressure or lipid profiles horses.

Cushing's associated laminitis

Another endocrinopathy, considered to be uncommon, yet recognized with increasing frequency over the past 20 years is equine Cushing's syndrome.[1] There are no epidemiologic studies, so the prevalence of this disease is not known. Equine Cushing's is caused by adenoma of the pituitary pars intermedia. Equine Cushing's syndrome shares with metabolic syndrome the propensity for laminitis, but it is not known what percentage of Cushing's horses have laminitis. The most widely seen clinical signs in Cushing's syndrome include long haircoat, abnormal shedding, and muscle wasting. Susceptibility to skin infections and slow wound healing are also seen in Cushing's disease.

Mechanisms of GCs explain these clinical signs. Breakdown of proteins (including skeletal muscle and collagen) that provide gluconeogenic precursors for maintenance of critical energy needs, results in muscle atrophy and skin changes. Integumentary changes in the hoof also appear to be GC induced. The insidious onset of Cushing's disease means that effects of long term endogenous GCs may not be readily apparent in experimentally induced laminitis. The role of GCs may be more important in Cushing's disease and metabolic syndrome than have been previously recognized.

Glucocorticoid effects in slow onset chronic laminitis could plausibly come from related effects of GC-induced changes in nutrient utilization and production. As GCs work to shift metabolism from general maintenance to "emergency" mode for sustaining critical functions, changes that would not be a problem in the short term can become pathologic over the long term. Altered protein metabolism could cause a general weakening of the laminar bond due to keratinocyte changes. Altered lipid metabolism could indirectly influence hoof laminar tissue. Perhaps fat deposits in locations remote from the feet are similar to omental fat in humans with metabolic syndrome. These fat deposits could contain metabolically active adipocytes that in turn affect the integumentary activity of 11B-HSD-1. Altered carbohydrate metabolism may reduce peripheral glucose utilization. This may affect the integument as a whole (explaining in part the skin infections) but would presumably have more serious consequences in the feet if it results in laminar bond weakening.

Hypothyroidism and laminitis

There is no scientific evidence to support a link between hypothyroidism and laminitis, nor is there any documented evidence that adult horses are susceptible to clinical thyroid disease. Despite these facts, many equine clinicians remain convinced of these links in horses presenting with obesity, lethargy, and laminitis. Experiments on effects of thyroidectomy in horses documented cardiac changes and basal metabolism changes that were reversible with supplementation.[35] However none of the alleged signs of clinical hypothyroidism were seen. What is more likely is that low levels of circulating thyroid hormones are the result, rather than the cause, of laminitis or other non-thyroidal illness.

At least 4 possible mechanisms may explain "hypothyroidism" in laminitic horses. First, GC effects can suppress thyroid hormones. Horses thought to be hypothyroid might actually have primary endocrinoapthies such as Cushing's or metabolic syndrome, both of which may be characterized by insidious onset GC-induced laminitis. Second, since gastrointestinal disease is often an initiating event in laminitis, protein-losing enteropathy could cause a lowering of total concentration of T3 and T4. Third, horses with pain, whether it is due to intestinal disease or laminitis, often become anorectic, which could lead to depressed thyroid hormone levels. Fourth, horses with foot pain are often treated with non-steroidal anti-inflammatories (NSAIDs). Binding of NSAIDs to plasma proteins can displace some of the normally bound thyroid hormones, lowering the total measured in radioimmunoassay. Experimental findings after 5 days of phenylbutazone administration showed enhanced T4 response to injection of TSH, indicating normal thyroid function.[36] Thus it is likely that NSAIDs decrease only the protein-bound hormones; with free hormone concentration remaining unaffected.

Despite the lack of evidence that thyroid medication is warranted in horses, clinical experience suggests some obesity-associated laminitic horses show improvement on supplementation. It is more likely to be a pharmacologic effect than a physiologic effect. Since thyroid hormones are known to potentiate B-adrenergic agonists, it is possible that beneficial effects come from vasodilation and enhanced digital perfusion.[37] Future research may

demonstrate effects of thyroid supplementation on laminitic horses, but at present, there is no medical justification for this popular clinical treatment.

Clinical relevance

Let's assume the precipitating event of laminitis has resolved. If the horse had Potomac Horse Fever, the acute illness passed. If the horse was eating an overload of carbohydrate the diet has now been modified. If the horse was diagnosed with Cushing's disease it is being controlled with appropriate drugs. Each of these cases represents a common scenario facing equine veterinarians. The patient is stable, yet chronic laminitis seems refractory to conventional treatments. One reason may be that the conventional pharmacological approach to laminitis management—NSAID administration[38]—potentiates the damaging effects of GC excess.[39] Adverse effects of NSAID therapy in horses, primarily gastro-intestinal ulceration and renal toxicity, may exacerbate or even indirectly trigger laminitis. The mechanism of anti-inflammatory action of NSAIDs and GCs are different, but one commonality is the inhibition of prostaglandin production. Gastrointestinal associated laminitis is seen acutely in experimental models. Mechanisms are different, but it is possible that chronic, even low dose use of NSAIDs ultimately has degenerative effects on laminar tissue with an effect similar to that of chronic endogenous GC excess.

A clinical challenge in treating chronic laminitis is to break the pain cycle without causing the horse to feel "too good" which can lead to overuse of the damaged feet (resulting in further damage). The pain cycle needs to be broken because effects of GC excess due to pain may worsen laminitis. Additionally, the altered posture of the typical "founder stance" places abnormal loads on the hoof wall which seem to compromise the new growth, contributing to the dished toe, underrun heel hoof shape seen in many chronic cases. But to date there is no satisfactory drug therapy protocol for chronic use in laminitis. Anti-inflammatory effects of both GCs and NSAIDs afford only short term pain relief at the expense of healing in the laminar tissues, which in the end causes protracted pain. Many of these horses are euthanized when they become refractory to pain control. More attention is being paid to mechanical stabilization of the digit as a way to reduce pain without compromising the healing process. Corrective shoeing and hoof trimming offer excellent options for managing the chronic stage of laminitis. Drug therapy for endogenous GC excess of Cushing's disease is not completely satisfactory but may be managed by pergolide in many horses.[40] For laminitis due to metabolic syndrome, the only truly successful therapy to date has been dietary management and exercise. The latter can be challenging in horses with chronic foot pain, but with appropriate farrier care these cases can often be well-managed. Prevention of adult onset obesity in the horse population may represent a major focus of client education in the future of equine veterinary practice.

One might speculate that pre-existing conditions predispose horses to laminitis, making them more susceptible to subtle GC effects. Subclinical digestive dysfunction may set the stage for systemic trigger factors to eventually cause laminitis that seems "sudden" to the owner because no warning signs were apparent. Subclinical laminitis is by definition difficult to study, but there has been some research documenting that it may be widespread among the equine population.[41,42] Perhaps there are pre-existing conditions locally, such as overgrown or imbalanced feet, that have caused cell damage at the laminar junction, predisposing basal keratinocytes to GC effects.

Summary

Having considered various possibilities for GC-induced laminitis, we now return to the original questions: Can GCs cause laminitis? Why are GCs not useful therapy for reducing the

pain and destruction caused by laminar inflammation? The scientific evidence on GCs and laminitis does not support a direct causal role between short-term GC excess (either endogenous or exogenous) and laminitis. However the long term GC elevation seen in disease or chronic stress situations does seem likely to play a role in the development and persistence of chronic laminitis. Molecular mechanisms of transcriptional inhibition result in anti-inflammatory effects, and transcriptional activation result in metabolic effects. Studies reviewed in this paper suggest that general pathways of GC effects (metabolic and anti-inflammatory) are likely to lead to a degenerative series of events in the laminar tissue.

Although administration of low or high dose steroid does not reliably induce acute laminitis, most studies lack of follow-up, therefore long term effects are not known. One study that did include follow-up found indirect evidence of subclinical laminitis. After an experiment on the pharmacokinetics and metabolic effects of triamcinolone, none of the horses exhibited clinical signs of laminitis; but during follow-up observation 2-14 months after the drug was administered, 4 of the 5 horses developed "hoof rings", macroscopic horn growth abnormalities known to be a sign of chronic laminitis.[26] Thus, GC effects may be subtle and contribute to insidious onset laminitis.

A wide range of events have been implicated as cortisol-induced laminitis triggers. Mechanisms include interactions among target tissues of the foot and different endocrine, paracrine or autocrine pathways. Integrity of the dermal-epidermal junction in the equine foot may be compromised by various GC-mediated events. Glucocorticoids effect vascular permeability, nutrient metabolism, and endocrine events associated with HPA activation. Clinical endocrinopathies in horses associated with laminitis, include Cushing's disease and insulin resistance, with hypothyroidism also believed by equine clinicians to play a role.

Better clinician and horse owner awareness of subclinical laminitis may offer increased opportunity to prevent endocrinopathic laminitis. Signs of hoof imbalance often can be seen grossly before any clinical signs of pain are exhibited by the horse. Earlier screening for metabolic syndrome may become part of routine health care for horses. Client education is important. Since management practices in young horses may predispose them to development of metabolic syndrome later in life, it is important for veterinarians to inform clients about emerging new knowledge regarding endocrinopathic laminitis.

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