

EMS, IR, ID, PPID, OST, TRH Stim- sorting out the equine endocrine alphabet soup

Jane Marie Manfredi, DVM, MS, PhD

Diplomate, American College of Veterinary Surgeons-LA

Diplomate, American College of Veterinary Sports Medicine & Rehabilitation (Equine)

Assistant Professor, Pathobiology and Diagnostic Investigation

Michigan State University, College of Veterinary Medicine

manfred1@msu.edu

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Equine Endocrine Disorders: Why do they matter?

Endocrine disease is the top cause of laminitis (inflammation of the lamina in the hoof which can result in separation of the coffin bone from the hoof wall- a painful and sometimes fatal condition) in the horse [1]. Equine Metabolic Syndrome (EMS) and Pituitary Pars Intermedia Dysfunction (PPID) are the top underlying conditions associated with endocrinopathic laminitis. They are often confused as they can occur concurrently and can share certain characteristics. The primary underlying concern with developing laminitis is elevated levels of circulating insulin. In healthy horses we know that infusing high levels of insulin can cause laminitis. The objective of this talk is to clarify the equine endocrine alphabet soup in regards to presentation of the major endocrine disorders, the currently advised testing, and updated insights into the pathophysiology behind the disorders including treatment.

PPID: Also called Equine Cushing's Disease, but preferably called PPID as the cells of Pars Intermedia of the Pituitary Gland are dysfunctional (the hypothalamus' dopaminergic neurons are degenerating). This is typically found in older horses (>20 years). The dysfunction of the Pituitary Adrenal Gland contributes to the high levels of adrenocorticotrophic hormone (ACTH) which likely interferes with the ability to regulate cortisol synthesis by the adrenal glands. PPID is most easily differentiated by the presence of symptoms, such as: abnormal sweating; delayed shedding; hypertrichosis, (long curly hair); laminitis; increased drinking & urination; infertility; lethargy; neurological deficits, including blindness; recurrent infections; skeletal muscle (especially topline) atrophy (https://sites.tufts.edu/equineendogroup/files/2019/12/2019-PPID_EEGbooklet.pdf).

Suggested Testing:

- Baseline ACTH measurement (moderate to advanced cases)- Blood can be collected at any time during the day into a Lavender/Purple Top Tube. Keep cold and centrifuge to separate the plasma ideally within 4-6 hours of the draw, before

shipping overnight on ice packs (sample can be frozen). There are seasonal differences, with elevated levels in the fall, so check your labs normal ranges.

- Thyrotropin-Releasing Hormone (TRH) Stimulation Test, measuring ACTH (early cases)[2]– Monitors ACTH levels before & after administering TRH (ask the Lab for seasonal reference ranges). If results are negative, repeat testing recommended in 6-12 months. Don't feed grain for 12 hours before testing, but hay and grass are okay. Collect a baseline specimen in a Lavender/Purple Top Tube; inject TRH IV, (0.5mg, less than 250kg), 1mg (greater than 250kg); Collect specimen exactly 10 minutes after injection. Process & submit multiple plasma samples together; to be received cold. Be sure to centrifuge and separate plasma from cells within 4 hours of collection, then transfer the plasma to a plastic vial. Refrigerate or freeze, be sure samples are shipped cold. ACTH is stable for 6 months in the freezer. This must be performed BEFORE oral sugar test (OST) and not within 12 hours after an OST.[3] The TRH used in this test is often obtained from a local veterinary university or compounding pharmacy.
- Some practitioners like to include a CBC/Chem Panel (Lavender/purple top tube CBC/ Chem Panel, Red top tube) and urinalysis (plain red top tube, (without serum separator gel)) as these horses and ponies are prone to secondary infections. Fecal egg counts are also often performed. Other tests used in the past such as the Dexamethasone Suppression Test are no longer in favor.

Recent Insights into Pathophysiology and/or Treatment:

Thyroid function has recently been investigated in horses with PPID and free thyroxine has found to be reduced likely due to glucocorticoids suppressing TRH[4]. Pergolide (Prascend)[5] is the mainstay of treatment as the only FDA approved drug to treat PPID. This is a dopamine agonist. For a pony start at 0.5 mg PO and for a horse start at 1 mg PO every 24 hours. If their appetite decreases, either cut the dose in half for a few days or stop treatment for a few days until it returns, then slowly increase the amount to the full 1 mg. Address secondary signs such as topline atrophy with resistance band training, deworming, farrier care and appropriate dental care. After two months, improvement in clinical signs can be addressed and re-testing can occur to monitor progress. Address weight loss if needed as per description below in EMS. Treat for EMS and insulin dysregulation as indicate below if it is present.

EMS:

EMS is known to affect a wide range of horses from 5-20 years of age. EMS is characterized by a combination of three main symptoms: Obesity +/- Regional Adiposity

in the neck, tail head & supra-orbital area (pouch above the eye); predisposition to Laminitis, both acute & chronic; Insulin Resistance (IR), and Insulin Dysregulation (ID).[6] They may also have dyslipidemia (abnormal amounts of lipids in the blood), hyperleptinemia, (elevated plasma leptin levels), arterial hypertension or increased system inflammation.

To explain the alphabet soup related to this condition, IR is a failure of insulin to stimulate glucose uptake by metabolically active tissues, (muscle, adipose, liver), when nutrients are introduced. This can result in elevated basal insulin levels. ID is abnormal insulin levels that can be exacerbated by incretin hormones released from the GI system into the bloodstream. In this sense, ID is the umbrella term for any resting or stimulated elevated insulin levels, while IR is specific to increased release of insulin due to tissue unresponsiveness. ID is generally diagnosed after oral testing. IR is a diagnosis most often made after intravenous testing.[7-9]

Since not all obese horses have EMS and not all EMS horses are obese,[10] an episode of laminitis is often the first indicator of the syndrome. Upon further testing, ID is revealed. It is the combination of these symptoms that yield the diagnosis of EMS. Some horses go on to develop PPID, but not all. Breeds that are predisposed to EMS are: Arabians, Welsh Ponies, Tennessee Walking Horses, Morgans, and Andalusians.[6, 11-13] Standardbreds and most, but not all, Quarter Horses are less susceptible.

Suggested Testing:

- Oral Sugar Test, (OST), Horse fasting for 3-12 hours before testing; Collect baseline either red top tube or purple top tube (check first what the lab you send samples to requests); give 0.15ml/kg Karo light corn syrup PO [14]; collect blood specimens at 60 & 90 minutes after Karo Syrup and re-draw blood samples using either red top or purple top tube: Purple top tube gently invert tube a few times to mix anti-coagulant/red top tube allow adequate time for clotting before centrifuge to avoid fibrin formation & to ensure adequate serum yield. After centrifuge immediately transfer plasma/serum into a plastic vial suitable for frozen storage & shipping. Assess the time points for insulin (glucose isn't diagnostically useful). The Karo syrup can be given by the owner to decrease your time spent on the farm. Karo syrup light specifically should be used as off brands have shown variable results.
- Insulin Tolerance Test (ITT)[15]- Blood samples drawn are immediately tested on a glucometer at baseline and 30 minutes after IV administration of insulin (0.1 IU/kg regular human recombinant insulin). This is a test for IR. It is nice as it can be performed on the farm, but it doesn't account for the incretin hormone release from the GI tract which can elevate insulin levels.

Recent Insights into Pathophysiology and Treatment:

The fecal microbiome is of great recent interest in EMS because lower microbiome diversity has been reported in EMS horses and is known to be present in humans with metabolic syndrome as well [16-18]. This decrease in diversity is thought to contribute to the continued disease state in humans [18] and ways to modulate the microbiome to ameliorate the disease are widely sought. There are several possibilities as to how shaping the microbiome can alter metabolic status. As processing of starch is critical for EMS/ID horses, with a high starch/non-structural carbohydrate (NSC) diet being implicated in laminitic events [19, 20], there is a critical need to modulate the microbiome to improve processing of nutrients.. Enteroendocrine cells are present throughout the gastrointestinal tract and are distributed along the mucosa surface. As such, they can interact with the microbiota in the lumen of the gastrointestinal tract which in turn can alter secretion of incretin hormones in response [21]. Increases in incretin hormones (GLP1 and 2) in response to a meal have been implicated in inducing a more pronounced (and undesirable) insulin response [9, 22-24]. Recently, Glucagon-like peptide 2 (GLP2) receptors were found to be upregulated in the small intestine of ID ponies [9]. GLP2 is secreted in response to meals with high non-structural carbohydrates; it enhances nutrient absorption and could contribute to elevated glucose and subsequently insulin levels in the ID animal [25]. *If we can alter the microbiome of EMS/ID horses to become more like that of metabolically normal horses, we can potentially affect insulin responses via changes in incretin hormone release in the gut.*

Current recommended treatment includes changes to diet, exercise, and additional supplementation. As far as diet, it's recommended to: eliminate all concentrates, feeding of grass hay with a NSC of <12%, no pasture turnout (or grazing muzzle used), weight loss (Start at 1.5% of current body weight hay (or complete feed) daily, Reassess every 30 days (ideal BCS 5/9), Soak hay in cold water for 60 minutes before feeding, Low carbohydrate (< 10% NSC) diet (NSC = simple sugar % + fructan % + starch %; Mineral/vitamin/protein ration balancer (be careful to look at starch content here).

Mild to moderate exercise including hills or resistance band training when possible can help lose weight and increase muscle mass which can help increase insulin sensitivity.

Supplementation can be used as an adjunct (not a replacement) to the above diet and exercise plans for treatment of EMS. Metformin has been of interest, and has been used clinically, with modest improvements in glucose and insulin concentrations seen in one study, and limited improvement in others, likely due to poor bioavailability.[15, 17, 20, 21] Short-chain fructo-oligosaccharides (sc-FOS) have been administered in combination with dietary restrictions resulting in some success in improving insulin sensitivity.[18]

Levothyroxine (Thyro-L) is recommended for horses with resistance to weight loss. Given the potential for heart issues secondary to thyroid oversupplementation in a recent study, albeit not published yet

(<https://www.horsetalk.co.nz/2019/03/20/danger-thyroid-supplement-fit-horses/#:~:text=The%20drug%20was%20not%20found,that%20can%20be%20career%20ending.>) avoiding this if possible may be ideal.

For a first line of supplementation, I am currently recommending Insulinwise from Kentucky Performance Products, a synergistic polyphenol (resveratrol) and amino acid blend including leucine for which I performed the research.[26] Although funded by the creator of the supplement, I determined the study design (we evaluated several well documented as being ID Morgans and Arabians) and analyzed and interpreted the data without company influence. I recommend 6 weeks of feeding Insulinwise in addition to other dietary modifications as above and then retesting with an OST. Many of the ID horses on the studies showed significant improvements such as: increased weight loss, higher adiponectin (an insulin sensitizing hormone) and lower insulin responses to the OST.[26] If the insulin response has decreased after 6 weeks of treatment, continue on with the supplement. Of note, insulins in response to an OST are highest in winter and spring (Macon et al., oral abstract 2018 AAEP), so be careful if your original test was in the summer or fall, as the follow up insulin may be higher but still decreased from what it would have been had supplementation not started.

Shared Characteristics:

Many horses and ponies may have these two endocrine disorders concurrently. They can share an outcome of laminitis, so many individuals confuse the two. Clinically, horses or ponies that have both seem to be more susceptible to laminitis or developing worse cases of laminitis, although this has not been irrefutably proven. For the reasons above, we recommend testing for both on horses that have breed predispositions to laminitis or animals who are showing clinical signs related to laminitis or either of these conditions.

Equine Endocrine Tips:

Check with the lab for tube & shipping requirements; use the same lab for testing as different insulin assays run at different labs can yield different results, even if on the same sample. Some laboratories have bundles for common endocrine related blood tests. If pulling samples out in the field, be sure to allow time in the schedule to adequately prepare samples for shipment to the lab. Ensure animal is not excited when drawing samples, i.e. If animal is shipping in, allow 30 minutes for them to settle before testing to ensure accurate test results. Don't test acutely painful/laminitic horses, this can lead to spurious results. A consensus of the most recent diagnostic approaches and treatments can be found at: <https://sites.tufts.edu/equineendogroup/>

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