VETERINARY MEDICINE

Equine Endocrine Diseases: A Refresher

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Outline

- Equine Pituitary Pars Intermedia Dysfunction
  - Pathophysiology
  - Clinical Signs
  - Diagnosis
  - Treatment and prognosis
- Equine Metabolic Syndrome
  - Definitions
  - Clinical Signs
  - Clinical Pathology
  - Diagnostics
  - Management and Treatment

Pituitary Pars Intermedia Dysfunction (PPID)

- *Equine Cushing's Disease* originally
  - One of the most common diseases of horses and ponies over 15
- Dramatic increase in aged horses
  - Increased testing and treatment
  - Much is still not completely understood

Pathophysiology

- Hallmarks
  - Hypertrophy, hyperplasia, microadenoma or macroadenoma
  - Increased secretion of propiomelanocorticotropin (POMC)
- Clinical signs likely due to increase POMC peptides
  - Loss of neuroendocrine function of adjacent tissues

Pathophysiology

- Loss of dopamine inhibition critical to pathology of PPID
- Dopamine and its metabolites have an 8 fold decrease in the pars intermedia of affected horses
- Oxidative Stress

Smith et al., Large Animal Internal Medicine, 6e, pg 1354

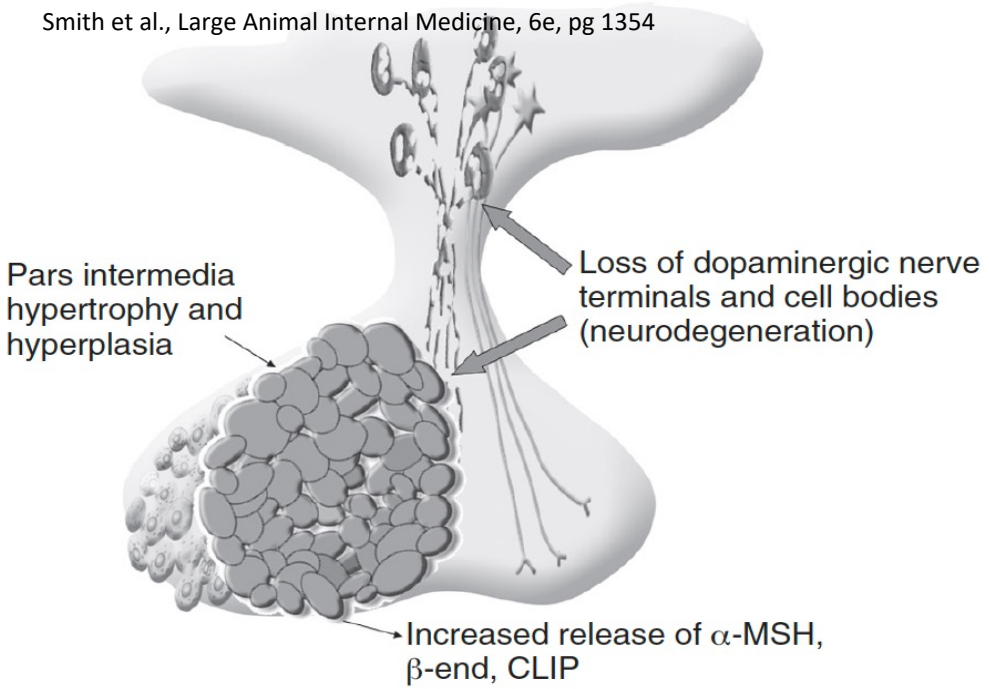


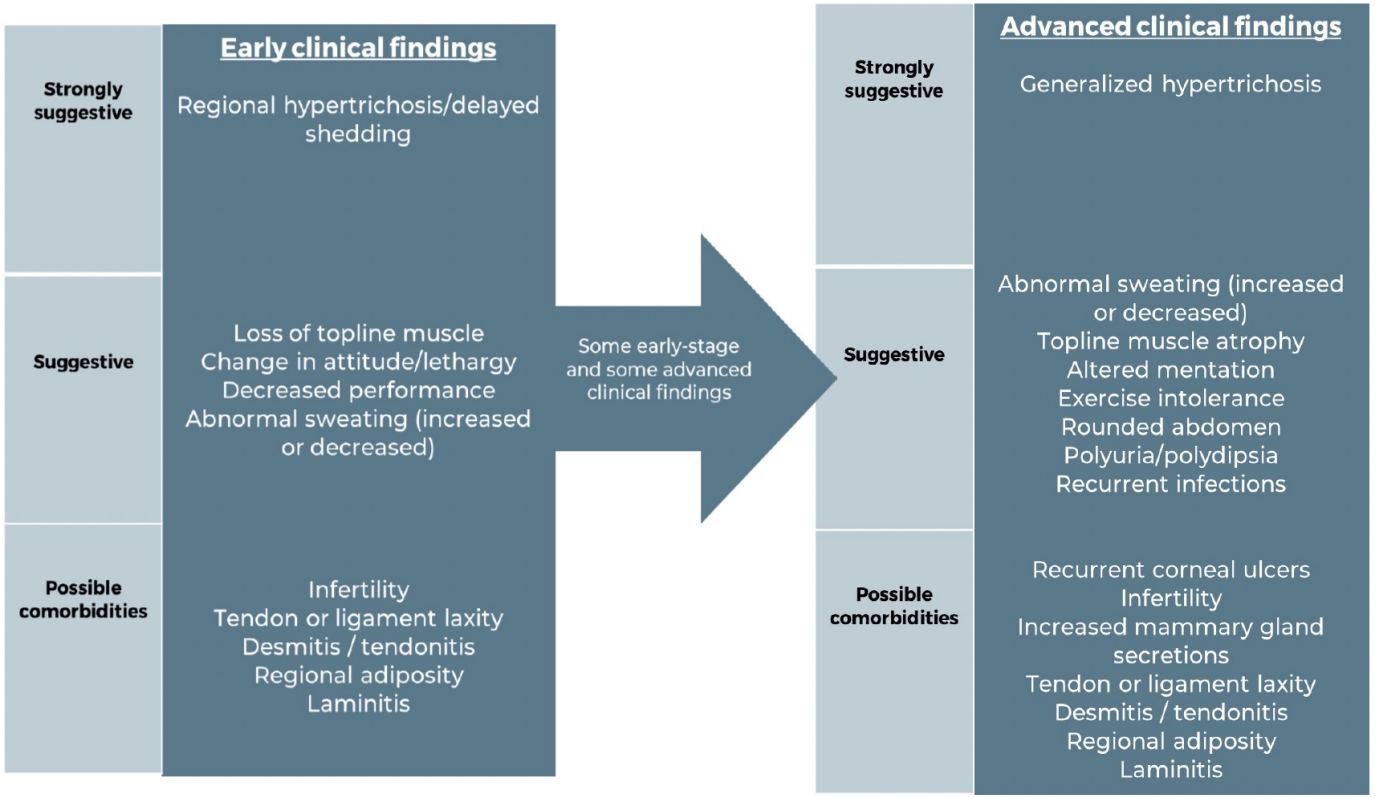
FIG. 41.3 Pathophysiology of equine pituitary pars intermedia dysfunction. Loss of functional dopaminergic periventricular neurons leads to a decrease in dopamine at the pars intermedia. This in turns results in dysinhibition of the melanotropes of the pars intermedia. The outcome is hypertrophy and hyperplasia of the pars intermedia and increased systemic release of the pars intermedia proopiomelanocortin (POMC)-derived peptides, α-melanocyte stimulating hormone (α-MSH), β-endorphin (β-end), and corticotropin-like intermediate lobe peptide.

Clinical Signs

- Hypertrichosis (hirsutism)
- Muscle loss (topline atrophy)
- Regional adiposity
- Laminitis
- PU/PD
- Secondary infections
- Lethargy
- Infertility
- Persistent lactation
- Exercise intolerance
- Sweating dysregulation
- Suspensory ligament breakdown

Figure 2 – Clinical progression of PPID

**Note: affected animals may have only one, several or many of the listed signs*



Hart et al. , EEG: *Recommendations for the Diagnosis and Treatment of Pituitary Pars Intermedia Dysfunction (PPID), 2021*

Diagnosis

- Currently 3 tests used in practice
  - Overnight dexamethasone suppression test (DST)
  - Baseline endogenous ACTH plasma concentration
  - Thyrotropin releasing hormone (TRH) stimulation test
- Seasonal variation in plasma ACTH concentrations
  - Inconsistent results to TRH stimulation from July – Dec
- Supportive testing
  - MRI
  - CT with contrast

DST

- Initially reported to 100% sensitivity and specificity
  - Not quite the whole story
- Intramuscular dexamethasone administered and ACTH from pars distalis suppressed
  - Unaffected horses
- Affected horses do not suppress due to production of ACTH from pars intermedia

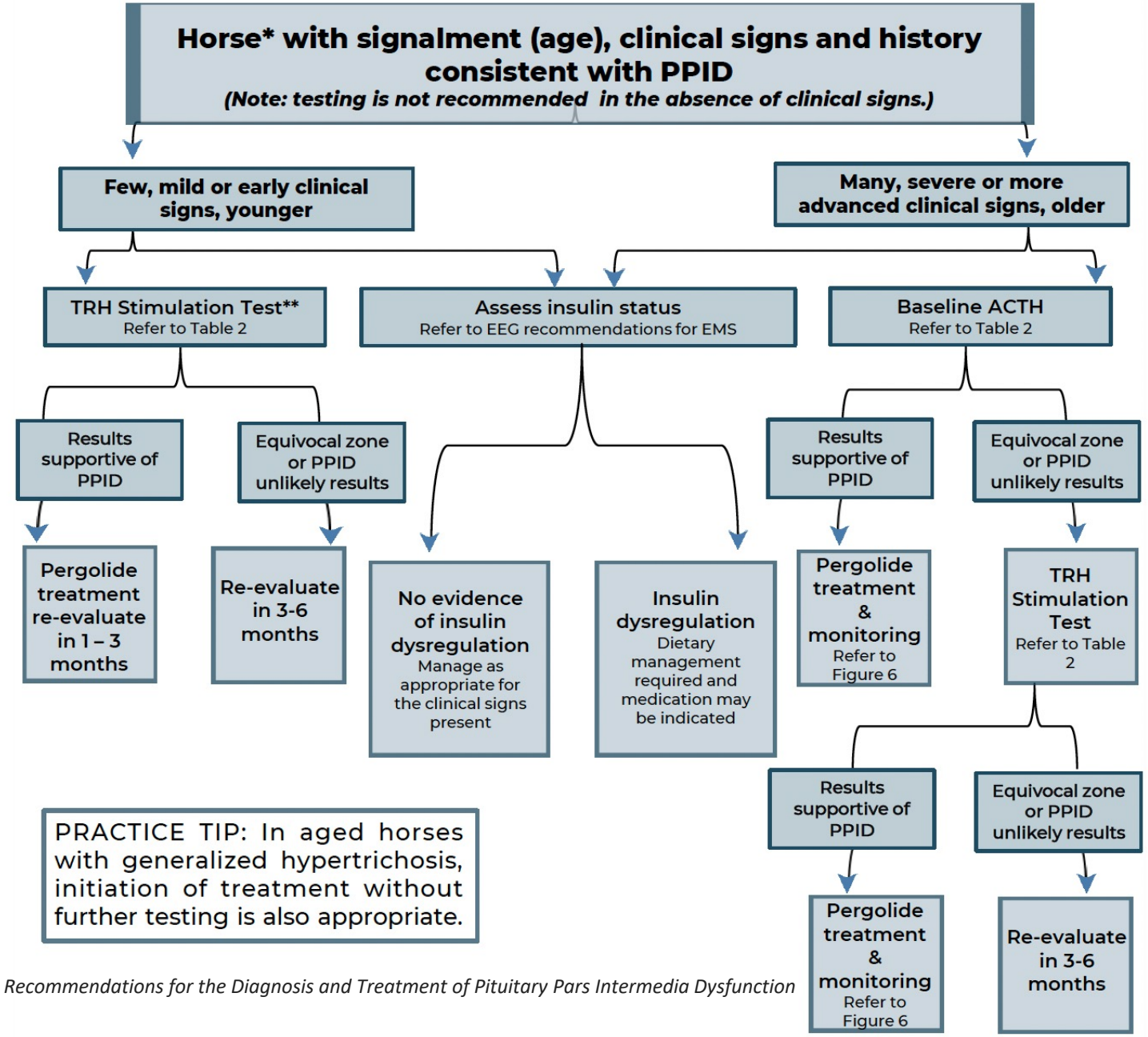
Endogenous ACTH

- Most common diagnostic
  - Initially sample handling was cited as hurdle
  - Plasma separation can be delayed 12 hours
- Seasonal variation in static and dynamic testing is well documented
  - Testing in autumn (Aug – Oct) yields much higher concentration
  - Established reference ranges for each season are available

TRH Stimulation Test

- Preferred method of testing for younger horses
  - Or any horse with few, mild, or early clinical signs
- TRH is known to be stimulate the pars intermedia
  - Initially cortisol was tested
  - Increased reliability using ACTH
- Currently only recommended for use during non-fall months
  - Only used to identify negative horses in fall months
    - High false positive rate during fall

FIGURE 3 - Algorithm for the diagnosis and management of PPID



Hart et al. , EEG: *Recommendations for the Diagnosis and Treatment of Pituitary Pars Intermedia Dysfunction (PPID), 2021*

Treatment

- Aimed at improving general health and reducing risk of disease complications
  - Body clipping hairy horses
  - Dietary management of horses with concurrent ID and EMS
  - Strategic parasite control plans
  - Dental and hoof care
- Pergolide (Prascend)
  - Initial dose 0.002mg/kg PO SID
  - Assess at 4 weeks; if needed increase in 0.001 – 0.002mg/kg increments
- Cyproheptadine
  - May be useful as an adjunct to refractory horses; 0.3 – 0.5mg/kg PO SID
  - Horses that show minimal response to 0.006mg/kg or higher of pergolide
  - Contraindicated in horses with history of seizures

Prognosis

- Prognosis is not well documented
- Many horses live for years
  - Especially with strong management
- Reports of many horses positively responding to pergolide for greater than 5 years

Equine Metabolic Syndrome

- A collection of risk factors for endocrinopathic laminitis
  - Insulin dysregulation, the key component
  - Increased adiposity
  - Hypertriglyceridemia
  - Altered adipokine production
  - Cardiovascular abnormalities
- Insulin dysregulation
  - Fasting hyperinsulinemia
  - Postprandial hyperinsulinemia
  - Tissue insulin resistance
- Most EMS horses are obese
  - Lean phenotype is recognized
- EMS vs PPID and their coexistence

Clinical Signs

- Most horses are obese (BCS 7 – 9)
  - ”Easy keepers” “good doers”
  - Cresty neck on PE
- Subclinical laminitis
  - Radiographs at initial examination

Clinical Pathology

- Hypertriglyceridemia and elevated GGT in some
  - CBC and other biochemical parameters normal
- Hyperglycemia
  - Diabetes mellitus when persistent
- Low resting tT3 and/or tT4 in some
  - Significance has been previously overstated
  - Most have normal TRH stimulation tests
  - Levothyroxine should be used in light of abnormal TRH stim tests
    - Or solely to accelerate weight loss for a short period of time

Diagnostic Testing

- Measures of adiposity
  - Body condition score
  - Cresty neck score
  - Ultrasound measurements of abdominal or subcutaneous fat
- Basal Insulin, glucose, leptin, and triglycerides
- Oral Sugar Test
- Insulin Tolerance Test

Diagnostic Testing

- Basal insulin
  - Low sensitivity, normal results does not rule out ID
  - Previously measured while fasting, now just withhold concentrate for 6h
  - Always measure glucose in conjunction
- Leptin
  - Positively correlated with BCS
  - Useful to monitor response to weight loss
  - Generally returns to normal before insulin in treated horses

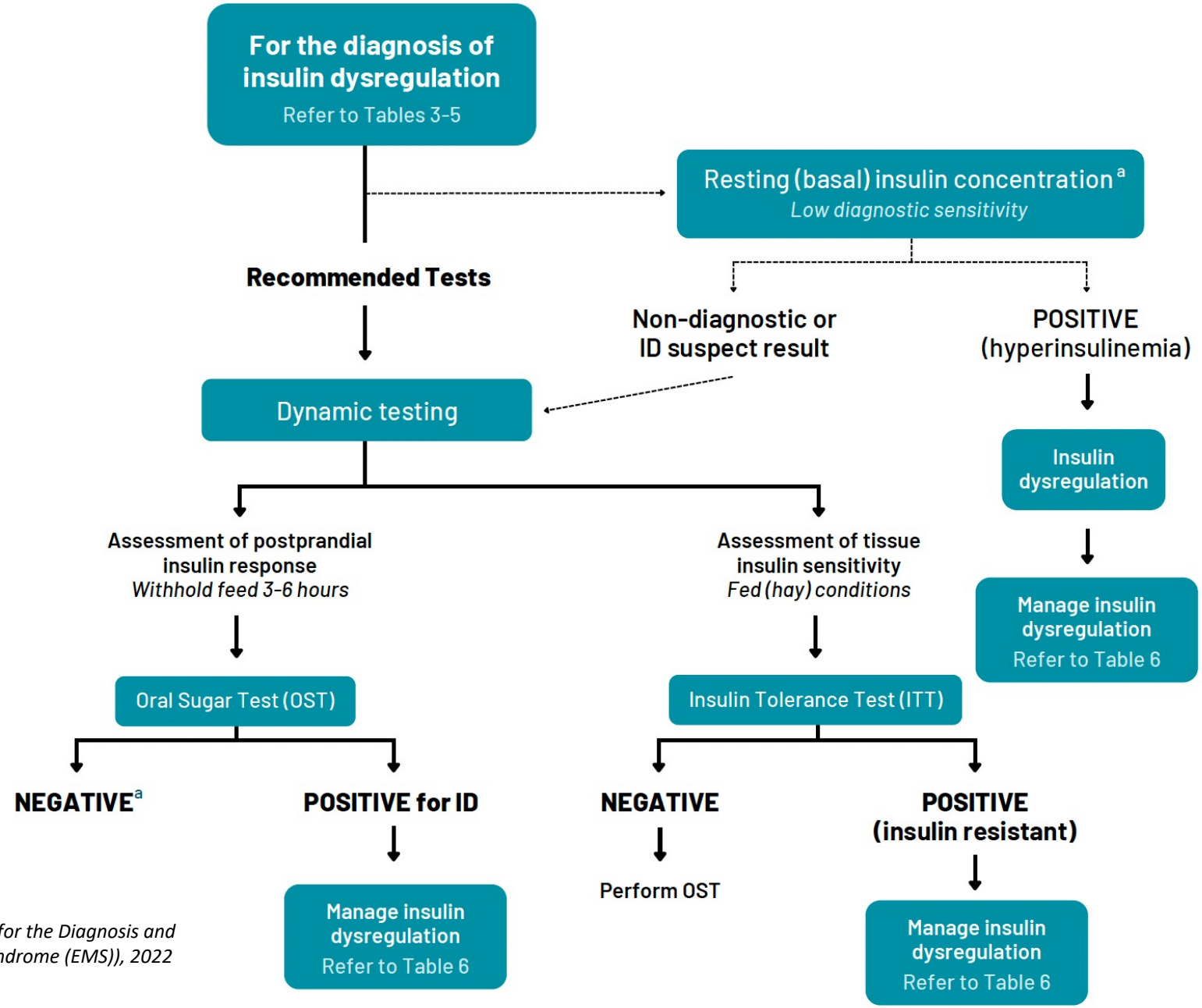
Diagnostic Testing

- Oral Sugar Test
  - Fast horse minimum 4h preferably 6h
  - Karo Light PO 0.15ml/kg
  - Blood for insulin and glucose testing at 60 and 90 min
- When used for monitoring only ID or non-ID is relevant
  - Repeatability of exact values is low
  - Can be managed by doing high dose 0.45ml/kg

Insulin Tolerance Test

- Convenient because does not require fasting
  - Glucose measured on farm with glucometer
- Cost of purchasing insulin
- Risk of hypoglycemia
  - Unlikely in most, more likely in lean phenotype EMS animals
- Measure initial blood glucose
  - Administer 0.1IU/kg Humulin
  - Measure BG again at 30 minutes
  - <50% reduction suggests ID
  - Additional BG sample at 15 minutes in high risk animals to prevent hypoglycemia

Figure 3 – Algorithm for detection of insulin dysregulation (June 2022)



Frank et al. , EEG: *Recommendations for the Diagnosis and Management of Equine Metabolic Syndrome (EMS)), 2022*

Management

- Diet!
  - Low sugar and starch
- Address modifying factors
  - PPID
  - Obesity
  - Inadequate exercise
- Obesity
  - Removal of concentrate
  - Limit pasture

Management

- Weight loss resistant horses
  - Low NSC forage at 1.5 – 2% of ideal BWT
  - Reassess monthly with weight tape or scale and BCS
  - May go as low as 1% ideal BWT if horse remains resistant
  - Trace minerals, protein, and vitamin E
- Maintenance diet

Treatment

- Two indication for pharmacologic therpay
  - Weight loss when diet has failed
  - Hyperinsulinemia in refractory cases
- Levothyroxine (high dose)
  - 0.1mg/kg daily in feed
  - While calorie restricting
- Sodium-glucose cotransporter (SGLT)-2 inhibitors
  - Velagliflozin: 0.3mg/kg PO SID
  - Canagliflozin 0.5mg/kg PO SID
  - Ertugliflozin 0.05mg/kg PO SID
  - DO NOT USE if horse are hypertriglyceridemic or for more than 3 months

Treatment

- Metformin 30mg/kg PO BID - TID
  - Only effective in a small percentage of horses
  - May lose efficacy over time
  - Can be administered at 50mg/kg
    - Oral irritation
  - Check insulin 2 hour post feeding before and after 7 days
    - To insure it is working in the patient

Conclusions

- Endocrine disease are common in mature horses
- PPID and EMS require long term management
- Overall long-term prognosis without severe laminitis is favorable
- Both diseases are hot research areas and there will continue to be improvement in diagnostic testing and pharmacologic management.

Questions?

References

1.) Stephen, M. R., et al. (2018). Chapter 16 - Disorders of the Endocrine System, Elsevier Inc: 1029-1138.

2.) Kelsey A. Hart, J. P. G., Diane Mcfarlane, Babetta Breuhaus, Nicholas Frank, Melody Anne De Laat, Cathy Mcgowan, Ramino E. Toribio, Dale E. Bauman, Robert J. Collier, Jessica A.A. Mcart, Daryl Nydam (2020). Chapter 41 - Endocrine and Metabolic Diseases. Large Animal Internal Medicine (Sixth Edition). D. C. V. M. Bradford P. Smith, Nicola Pusterla, Mosby. 1: 1352-1420.e1312.

3.) Vaughn, S. A., et al. (2022). "Circulating Hypothalamic-Pituitary-Adrenal Axis Hormones and Insulin Concentrations in Horses and Ponies." Journal of equine veterinary science 111: 103810-103810.

4.) Thane, K., et al. (2022). "Effect of early or late blood sampling on thyrotropin releasing hormone stimulation test results in horses." Journal of veterinary internal medicine 36(2): 770-777.

5.) Durham, A. E., et al. (2022). "The effect of month and breed on plasma adrenocorticotropic hormone concentrations in equids." The veterinary journal (1997) 286: 105857-105857.

6.) Durham, A. E. (2022). "The effect of pergolide mesylate on adrenocorticotrophic hormone responses to exogenous thyrotropin releasing hormone in horses." The veterinary journal (1997) 285: 105831-105831.

7.) Tatum, R. C., et al. (2021). "Evaluation of the sensitivity and specificity of basal plasma adrenocorticotrophic hormone concentration for diagnosing pituitary pars intermedia dysfunction in horses: A systematic review." The veterinary journal (1997) 275: 105695-105695.

8.) Steel, N. L., et al. (2022). "Management of pituitary pars intermedia dysfunction in practice: A clinical audit." The veterinary journal (1997) 289: 105899-105899.

9.) Warnken, T., et al. (2023). "Palatability, glycemic, and insulinemic responses to various carbohydrate formulations: Alternatives for the diagnosis of insulin dysregulation in horses?" Journal of veterinary internal medicine.

10.) Xue, C., et al. (2022). "Pharmacokinetic properties of pergolide mesylate following single and multiple-dose administration in donkeys (Equus asinus)." Equine veterinary journal.

11.) Stoeckle, S. D., et al. (2022). "Plasma Amino Acids in Horses Suffering from Pituitary Pars Intermedia Dysfunction." Animals (Basel) 12(23): 3315.

12.) Sundra, T., et al. (2022). "Preliminary observations on the use of ertugliflozin in the management of hyperinsulinaemia and laminitis in 51 horses: A case series." Equine veterinary education.

13.) Macon, E. L., et al. (2022). "Seasonal Insulin Responses to the Oral Sugar Test in Healthy and Insulin Dysregulated Horses." Journal of equine veterinary science 113: 103945-103945.

14.) Kellon, E. M. and K. M. Gustafson (2022). Use of the SGLT2 inhibitor canagliflozin for control of refractory equine hyperinsulinemia and laminitis. 12: 511-518.

15.) Hart et al. (2021). "Recommendations for the Diagnosis and Treatment of Pituitary Pars Intermedia Dysfunction (PPID)." Equine Endocrinology Group Guidelines 1-14. https://sites.tufts.edu/equineendogroup/

16.) Frank et al. (2022). "Recommendation for the Diagnosis and Management of Equine Metabolic Syndrome (EMS)." Equine Endocrinology Group Guidelines 1 – 20. https://sites.tufts.edu/equineendogroup/

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