Equine Endocrine Diseases

with

Dr Rachel Tan

BVSc MS Dip Vet Clin Stud Cert Vet Ac (CSU) Grad Cert (Tertiary Teaching) MACVSc Dipl ACVIM (Large Animal)

Specialist - large Animal Medicine

Senior Lecturer

James Cook University, QLD 4811
Equine Endocrine Disease. The big 2 – PPID and EMS

Dr Rachel Tan
BVSc DVCS MACVSc CertVetAc(CSU) MS DipACVIM GradCertEd
Senior Lecturer, Specialist in Large Animal Medicine,
School of Veterinary & Biomedical Sciences, James Cook University, Australia.

Introduction

• Previously considered to occur less frequently due to absence of defined clinical syndromes and accurate diagnostic testing
• Some endocrine diseases such as diabetes insipidus and hyperthyroidism are extremely rare findings
• Concurrence of endocrinopathies and laminitis significant – 89% cases
• Improved management and increased life span has increased focus on geriatric care with significant recent discoveries in diagnosis and treatment of endocrine dysfunction in horses

Pituitary Pars Intermedia Dysfunction (PPID)

• Most commonly diagnosed equine endocrine disorder
  - 22% geriatric horses
  - 70% of laminitis cases
• Formerly known as “Equine Cushing’s Disease”, but pathophysiology significantly different from small animals
Clinical presentation
• Range 7-42y but 81% horses >15y
• Ponies and Morgan horses over-represented
• No sex predisposition

Diagnosis
1. Clinical signs
2. Clinical Pathology
3. Endocrine testing
4. Post mortem (gold standard)

1. Clinical signs
• Hypertrichosis (Hirsutism) (84%)^4^4
  ❖ Equine Dermatology: Although the hair coat abnormality has classically been referred to as hirsutism, this is inappropriate. Hirsutism refers to hair growth in women in areas of the body where hair growth is under androgen control and in which normally only postpubescent males have terminal hair growth (e.g., mustache, beard, chest). The hair coat abnormality in PPID is properly called hypertrichosis, which specifically refers to hair density or length beyond the accepted limits of normal for a particular age, race, or sex.
  ❖ Long, curly hair coat which fails to shed - unknown cause → telogen arrest of hair follicles
  ❖ Almost all horses with hirsutism have abnormal pituitaries (specificity 95%^5^5), but not all with abnormal pituitaries have hirsutism (sensitivity 71%^5^5)
  ❖ Initially may be restricted to lower jaw, base of neck, palmar/plantar aspect distal limbs
  ❖ Progression to generalized hirsutism
  ❖ Occasionally dark hair coats → lighter colour

Table 2
Clinical signs in 159 horses and ponies with pituitary pars intermedia dysfunction

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Hirsutism</td>
<td>47%^b^</td>
<td>94%</td>
<td>100%</td>
<td>100%</td>
<td>95%</td>
<td>83%</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>NR</td>
<td>59%</td>
<td>67%</td>
<td>NR</td>
<td>14%</td>
<td>33%</td>
</tr>
<tr>
<td>Weight loss/muscle wasting</td>
<td>NR</td>
<td>88%</td>
<td>NR</td>
<td>38%</td>
<td>50%</td>
<td>47%</td>
</tr>
<tr>
<td>Abnormal fat distribution</td>
<td>NR</td>
<td>12%^c^</td>
<td>67%</td>
<td>19%^c^</td>
<td>9%^c^</td>
<td>29%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>NR</td>
<td>82%</td>
<td>NR</td>
<td>NR</td>
<td>45%</td>
<td>NR</td>
</tr>
<tr>
<td>Chronic laminitis</td>
<td>NR</td>
<td>82%</td>
<td>NR</td>
<td>24%</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>Polyuria and polydipsia</td>
<td>26%</td>
<td>76%</td>
<td>17%</td>
<td>NR</td>
<td>32%</td>
<td>34%</td>
</tr>
<tr>
<td>Chronic infections</td>
<td>32%</td>
<td>48%</td>
<td>33%</td>
<td>NR</td>
<td>27%</td>
<td>NR</td>
</tr>
<tr>
<td>Neurologic signs, including seizures</td>
<td>21%</td>
<td>6%</td>
<td>50%</td>
<td>10%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR, not reported.
^a^ Reports in which pituitary gland pathologic findings were confirmed by postmortem examination.
^b^ The low frequency of hirsutism in this report may be a result of the fact that it was a pathologic study in which clinical signs were not comprehensively described.
^c^ Reports describing only supraorbital fat deposition.
• Laminitis (50%)
  ❖ 89% laminitis cases in one study had endocrine disease – 1/3 PPID
  ❖ Many postulated causes: hyperinsulinaemia, alterations in cortisol metabolism, endocrine function of fat cells, decreased laminar tissue glucose utilisation

• Lethargy
  ❖ Docility, increased pain tolerance, poor performance
  ❖ Increased β endorphin effect

• Hyperhydrosis
  ❖ Excessive sweating
  ❖ Commonly noted over neck and shoulders
  ❖ Thermoregulatory response or effect of POMC peptides

• Weight loss, muscle wasting (abdominal muscle weakness and stretching = “roundness” of abdomen)

• Polyuria, polydypsia (PU/PD)
  ❖ Osmotic diuresis
  ❖ Partial neurogenic diabetes insipidus due to neurohypophysis destruction by expansion of pars intermedia
  ❖ Central stimulation of thirst by hypercortisolism

• Chronic Infections, delayed wound healing

• Regional Adiposity
  ❖ Neck crest, tail head, prepuce, supraorbital, upper thorax/abdomen “buffalo torso”
  ❖ Cortisol enhanced fat deposition

• CNS dysfunction
  ❖ Blindness – compression of optic chiasm by enlarged pituitary
  ❖ Ataxia
  ❖ Seizures

• Persistent lactation, infertility

• Musculoskeletal effects
  ❖ Osteoporosis?
  ❖ Hypertrophic osteopathy
  ❖ Suspensory apparatus breakdown

2. Clinical pathology

• Non specific

• Haematology
  ❖ May include mild anaemia, absolute or relative neutrophilia, absolute or relative lymphopaenia
  ❖ One or more of these abnormalities found in 1/3+ cases

• Biochemistry
  ❖ Moderate hyperglycemia 25-75% cases
  ❖ May include elevated liver enzyme activity, hypercholesterolemia, and hypertriglyceridaemia - may reflect hepatic fat infiltration in more advanced cases or degree of steroid hepatopathy
  ❖ Occasionally hyperlipaemia

• Urinalysis
  ❖ Glucosuria uncommon unless hyperglycaemia (>175-200 mg/dL) present
  ❖ Occasionally ketonuria
3. Diagnostic testing

- In practice, diagnosis of PPID is most commonly made by observation of hirsutism and other concurrent clinical signs in older equids
- Diagnosis by clinical examination likely to be accurate in advanced cases, but challenging in less severely affected horses
  - Under-recognized in younger horses
  - Disease recognition may be important in prevention of laminitis in risk groups
- Endocrine testing

Endocrine testing of limited/no value in PPID diagnosis

- Basal Cortisol
  - Resting cortisol concentration not significantly different
  - Non-functional ACTH production?
  - Loss of diurnal rhythmicity (<30% variance morning > evening) may be present but subject to external stressors. May have some use as a screening tool
- ACTH Stimulation test
  - Adrenocortical hyperplasia rare with PPID
  - No difference between PPID affected and normal horses
- Urinary corticoid:creatinine
  - Corticoid/creatinine ratio ranged from 7.5 – 52 x10 PPID horses to 4.7 – 16 x10 normal horses
  - Ratio >20 x10 had a sensitivity of 100%
  - Not used as sole diagnostic test as overlap with normal horses
- Salivary [cortisol]
  - Only free fraction of cortisol secreted into saliva thus, substantially lower than [plasma]
  - Diurnal: evening > morning
  - Basal [cortisol] higher in three PPID-affected horses (range: 3.6–6.9 nmol/L), minimal suppression by dexamethasone and exaggerated response to ACTH administration
  - Further investigation required
- Basal insulin and insulin sensitivity
  - Hyperinsulinemia is commonly seen (CLIP potent pancreatic β cell secretagogue)
  - Not specific as also occurs with equine metabolic syndrome (EMS)
  - Wide fluctuations in concentration and false positives with fasting
- Pituitary Imaging
  - CT
  - Only 2/3 of cases have pituitary macroadenomas (>10mm diameter)
  - Unknown number of normal animals have pituitary enlargement for reasons unrelated to PPID
  - No change in size despite treatment and improvement clinically and on DST

Endocrine testing of value in PPID diagnosis

- Post mortem = gold standard
- Dexamethasone Suppression Test (DST)
- Basal ACTH
- Thyrotropin Releasing Hormone (TRH) stimulation
- Combined DST and TRH
- α-MSH
- Domperidone Challenge test
• **Dexamethasone Suppression Test (DST)**
  - Controversial “gold standard” test
  - Previously the most practical and best-validated supportive endocrinologic test for confirmatory diagnosis
  - Recent debates over utility due to questionable functionality of ACTH produced by pars intermedia
  - Currently not recommended in the USA for diagnosis (2012)
  - **Overnight Test**
    - Basal [cortisol] late afternoon, typically 5pm
    - Administer dexamethasone 40 μg/kg IM
    - [Cortisol] 17h-19h after dexamethasone, typically 10am-12pm the next day
  - **Positive result** = incomplete cortisol suppression, >30 pmol/L (>10 μg/dL)
  - Result of partial suppression unknown
  - **Season effects on HPA Axis**
    - Dexamethasone fails to suppress ACTH release in normal horses in autumn \( \rightarrow \) False positive\(^{10}\) or early disease?
    - Test recommendation in Autumn as early cases have ↑ response
  - **Laminitis** - Reduce dexamethasone dose to 20 μg/kg

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>Dybdal NO</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>JAVMA 1994</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frank N</td>
<td>65%</td>
<td>86%</td>
</tr>
<tr>
<td>JVIM 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beech J</td>
<td>23-66%</td>
<td>100%</td>
</tr>
<tr>
<td>JAVMA 2007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• **Elevated basal ACTH**
  - Cutoff point >35pg/mL (7.7pmol/L), >47pg/ml (10.3pmol/L) Autumn\(^{11, ACVIM 2012}\)
  - Variable pulsatile secretion
  - Diurnal effects - morning > evening
  - Seasonal effects – Autumn peak in normal horses\(^{12}\)
  - If elevated at initial diagnostic evaluation, serial measurement may be a useful single-sample measurement to monitor for response to treatment
  - **Sample collection**
    - Collect at any time of day – may collect 2 samples 15 minutes apart and pool plasma
    - Venipuncture into EDTA (purple-top) tubes and refrigerated
    - Centrifuged within 8 hours with supernatant plasma harvested
    - Ship overnight with ice packs or freeze and submit on dry ice if analysis not within 24 hours
    - Preservatives not required
    - Testing laboratory validated for equine specific ACTH
  - **Testing in Australia**
    - Vetnostics: protocol in green, ACTH $165 (including GST)
    - IDEXX endogenous ACTH (EN2): Collect blood in EDTA tube and submit for analysis within 24h – do not centrifuge or freeze, $113.74 (including GST)
    - Freezing unnecessary if sample submitted and analysed within 24h
Thyrotropin Releasing Hormone (TRH) stimulation*

- TRH is a releasing hormone for several pituitary hormones including ACTH - relatively greater expression of TRH receptors on melanotropes than corticotropes
- 1mg TRH IV
- Increase in [ACTH]
  - PPID horses significantly higher
  - Positive result = > 100pg/ml @ 10 mins and >35pg/ml @ 30 mins
- TRH source in Australia
  - $140 for 50gm – flat rate of shipping $35 ($3.50 per dose)
  - Guaranteed for 1 year from delivery date
  - Dissolved in sterile 0.9% saline (1 ml)
  - 0.2μm syringe filter (Minisart, pack 50 = $292, $6 each) and stored in sterile Eppendorf tubes at -70°C until use intravenously
- Increase in concurrent [Cortisol] no longer considered useful
  - Positive result = 30% [cortisol] increase 15-90mins post TRH
  - However, large variability in resting [cortisol]
  - Combine with DST
• Combined DST and TRH Stim
  1) Dexamethasone 40μg/kg administered 3h before TRH to suppress [cortisol] in both PPID-affected and normal horses
  2) [cortisol] measured before TRH
  3) TRH 1mg IV
  4) [cortisol] measured 30mins post TRH
  - Normal horses no increase [cortisol], PPID increased >66%
  - Sensitivity 88%, Specificity 76%

• α MSH
  - No circadian rhythm for αMSH or effects from reproductive status
  - Reference range <35pmol/L?
  - Higher in ponies?\(^{12}\)
  - Positively correlated with BCS
  - Significant seasonal effect with increase in fall - ponies 11x, horses 2x\(^{12}\)
  - Higher in Autumn (Sept-Oct USA) but less false positives than ACTH
  - Research only, no commercial assay – more work required to define cut off values

<table>
<thead>
<tr>
<th></th>
<th>Jan-Jun (Spring)</th>
<th>Sept (Autumn)</th>
</tr>
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<tbody>
<tr>
<td>Horses</td>
<td>9.5-15.9</td>
<td>27-58</td>
</tr>
<tr>
<td>Ponies</td>
<td>3-19</td>
<td>40-185</td>
</tr>
</tbody>
</table>

• Domperidone challenge test
  - 1.5-5.0 mg/kg Domperidone PO = dopamine antagonist
  - Removes any remaining dopamine inhibition on melanotropes in PPID horses resulting in >2x increase in [ACTH] 4-8h post domperidone
  - Combined with TRH administration\(^{14}\)
    - Increased accuracy
    - Elevations in [ACTH] and [αMSH]
    - [αMSH] >30/50 pmol/L not superior to [ACTH] ≥36pg/ml before/after TRH
  - No increase detected in normal horses
  - More studies required to determine sensitivity, specificity or seasonal effects

Diagnosis in clinical practice
• HIRSUTISM! + other clinical signs
• Dexamethasone Suppression Test (DST)??
• Basal ACTH
• TRH stimulation test

Treatment
1) Management
- Dental care – high morbidity associated with age-dependent dental attrition because of combined effects of immune compromise and osteoporosis
- Anthelmintics – higher FEC
- Foot care – laminitis prevention and management
- Nutrition – concomitant insulin resistance
- Coat clipping – thermoregulation
• Antimicrobials – low-grade or subclinical infections, especially lower urinary and respiratory tracts

2) Dopamine agonists
• Pergolide mesylate
  ❖ Drug of choice
  ❖ Initial dose 0.002mg/kg PO q24h (i.e. 1mg per 500kg) – reduced side effects if start at 0.5mg per 500kg and increase by 0.25mg every 3 days
  ❖ Slow increase in 0.5-1mg increments if required up to 0.01mg/kg
  ❖ Dose adjustments every 6-12 mths due to slow response – some horses improve if total dose is split and administered BID
  ❖ Commercial versus generic
    ✓ Prascend (USA), Ranvet (AUS)
    ✓ Generic – drug separation in liquid and powder, heat and light intolerant
    ✓ Decreased dosage of commercial products?
  ❖ 85% favourable outcome, 35% normalisation of DST, normalisation of ACTH?
  ❖ Adverse effects – depression, anorexia, ataxia
  ❖ Seasonal treatment?? – start one month before Autumn
  ❖ No need to taper dose to discontinue
  ❖ Wear gloves
  ❖ Permax – human Parkinson’s drug voluntary FDA withdrawal due to heart valve damage – wear gloves
• Bromocriptine - poor oral bioavailability, not recommended
• Chasteberry (Vitex agnus-castus)
  ❖ 60mls per day
  ❖ No controlled studies on efficacy
  ❖ Used in humans for reproductive problems associated with elevated plasma [prolactin]
  ❖ 2 advanced cases showed minimal improvement, several cases worsened or failed to improve

3) Serotonin antagonist
• Cyproheptadine
  ❖ Second treatment drug in conjunction with pergolide
  ❖ 0.6-1.2mg/kg PO q24h
  ❖ 25-43% clinical improvement, 15% normalisation of DST
  ❖ May not be as effective as management adjustments

4) Competitive inhibitor of adrenal steroidogenesis
• Trilostane - inhibits the enzyme 3b-hydroxysteroid dehydrogenase
  ❖ 0.4-1.0mg/kg PO q24h
  ❖ Adrenocortical hyperplasia in only 20% of PPID-affected equids, therefore inhibition of adrenal biosynthesis of cortisol may not be particularly effective in most patients
  ❖ Although TRH/DEX tests improved by 30 days of treatment endocrinologic abnormalities did not become normal
  ❖ Consider as an adjunct in cases which pergolide ineffective
5) Dietary supplements
   - Magnesium and Chromium
     - Mg deficiency a risk factor for insulin insensitivity and type 2 diabetes in humans,
     - Cr Improves carbohydrate metabolism and insulin sensitivity
     - Supplementation with chromium tripicolinate has demonstrated to increase
       glucose uptake during a glucose tolerance test in normal yearlings (175-500 μg/kg
       concentrate)
     - Recent study in 2010 reported no alterations in morphometric measurements,
       blood variables, resting insulin concentrations or insulin sensitivity in laminitic
       obese horses

Treatment plan and evaluation
   - Management changes
     - Initial treatment with pergolide mesylate at 0.002 mg/kg PO q24h (1mg/500kg)
     - Rate of clinical improvement is higher than that for normalization of hyperglycemia and
       endocrinologic test results (80% vs 33%)
     - Endocrinologic testing
       - DST or plasma ACTH concentration
       - 1 month after change in medication or dose
       - Twice yearly if stable
     - If no improvement within 6-8 wks, increase daily dose by 0.002 mg/kg monthly up to a
       total dose of 0.01 mg/kg
     - If no, or limited response, with pergolide at 0.004-0.006 mg/kg and endocrinologic test
       results remain abnormal → 0.3-0.5 mg/kg cyproheptadine added

Prognosis
   - Lifelong condition, prognosis fair-guarded
   - Minimal long term studies
     - Clinical and laboratory data not associated with survival
     - 50% survived 4.5 years after diagnosis with clients satisfied with quality of life
     - Of those euthanised, 76% due to conditions associated with PPID
     - 97% owners who treated their animals would treat a second horse
Equine metabolic syndrome (EMS) first recognised in 2002 when connection proposed between obesity, insulin resistance, and laminitis

- Alternate names - peripheral Cushing’s syndrome, pre-laminitic metabolic syndrome

- Since July 2010, consensus by ACVIM defining EMS
- EMS adopted because of similarities with Metabolic Syndrome (MetS) in humans - collection of risk factors assessed to predict occurrence of coronary artery disease and type 2 diabetes mellitus

Pathophysiology

- Environmental (diet, level of physical activity, season) and intrinsic (genetic)
- Enhanced metabolic efficiency
  - Evolutionarily adapted to survival in nutritionally sparse environments
  - “Ferals” retain strong seasonality in appetite and body condition → weight gained in summer lost during winter

1) Adiposity
- Domesticated equids → chronic state of overnutrition, including improved pastures → progressive obesity
- Lipotoxicity
  A. Intracellular lipid accumulation
  B. Altered adipokine secretion
    - Adipose tissue functions as an endocrine organ producing many hormones (adipokines)
    - ↑Leptin and and leptin resistance - satiety factor which signals hypothalamus that state of energy excess exists within adipose tissues
    - ↓ Adiponectin: insulin-sensitizing adipokine
  C. Inflammatory mediator production
    - TNFα, IL-1, IL6 released by macrophages
    - Altered cortisol production via ↑11bHSD1 activity?
    - Self perpetuating cycle of enhanced inflammation, adipokine synthesis and secondary acute phase protein synthesis by the liver
    - Obesity in people characterized by state of chronic low-grade inflammation
2) Hyperinsulinaemia and Insulin resistance (IR)
   • Unknown if obesity induces IR or IR horse more predisposed to obesity
     ❖ Feeds rich in starches and simple sugars create a glycaemic response that is
difficult for IR horse to accommodate
   • 2 primary theories linking obesity to IR
     ❖ Down-regulation of insulin signaling pathways induced by adipokines/ cytokines
     ❖ Accumulation of intracellular lipids in insulin-sensitive tissue such as skeletal
muscle (lipotoxicity) or non-adipose tissue - altered normal cellular functions,
including insulin signaling
   • Hepatic insulin resistance
     ❖ IR → hepatic lipidosis
     ❖ ↑ GGT and AST
   • Peripheral insulin resistance
     ❖ Reduction in insulin activity on target tissues
     ❖ Glucose transporter function (GLUT4) impaired

3) Laminitis
   • Still unclear why IR predisposes to laminitis
   • Theories
     ❖ ↑ risk associated with CHO overload
     ❖ Impaired glucose delivery or uptake by laminar cells
     ❖ Intestinal trigger by movement of gut derived factors inducing a systemic
inflammatory response
     ❖ Altered blood flow or endothelial cell function within digital vessels
     ❖ Matrix metalloproteinase activation by glucose deprivation or reactive oxygen
species

Clinical presentation
   • Breed predisposition
     ❖ Ponies, miniature horses, donkeys,
     ❖ Morgans, Paso Finos, Norwegian Fjord
   • No sex predilection
   • Genetically predisposed horses recognized as “easy keepers” at young age and some are
obese by 3-4yrs, laminitis often develops at 5-15yrs
   • Most horses out on pasture in spring during rapid growth when laminitis is first detected
   • Horses of any breed can develop EMS if they become obese
   • Suggested that risk of laminitis increases over time if horse remains obese
   • EMS horses can subsequently develop PPID, particularly at a younger age

Clinical signs
   • Laminitis
   • General obesity – BCS ≥ 7/9
• Regional adiposity
  ❖ Cresty neck – neck score (≥ 3/5) negatively correlated with insulin sensitivity\textsuperscript{16}

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No visual appearance of a crest (tissue apparent above the ligamentum nuchae). No palpable crest</td>
</tr>
<tr>
<td>1</td>
<td>No visual appearance of a crest, but slight filling felt with palpation</td>
</tr>
<tr>
<td>2</td>
<td>Noticeable appearance of a crest, but fat deposited fairly evenly from poll to withers. Crest easily cupped in one hand and bent from side to side</td>
</tr>
<tr>
<td>3</td>
<td>Crest enlarged and thickened, so fat is deposited more heavily in middle of the neck than toward poll and withers, giving a mounded appearance. Crest fills cupped hand and begins losing side to side flexibility</td>
</tr>
<tr>
<td>4</td>
<td>Crest grossly enlarged and thickened, and can no longer be cupped in one hand or easily bent from side to side. Crest may have wrinkles/creases perpendicular to topline</td>
</tr>
<tr>
<td>5</td>
<td>Crest is so large it permanently droops to one side</td>
</tr>
</tbody>
</table>

Fig. 1. Illustrations of individual cresty neck scores.

• Regional adiposity
  ❖ 2009 - mid-neck circumference to height at withers ratio in ponies with cutoff >0.71\textsuperscript{15}
• Regional adiposity
  ❖ Fat deposits around tail head, sheath, supraorbital fossa
  ❖ SC masses
• Laminitis
• Colic – pedunculated lipoma formation at early age
• Infertility in mares

**Diagnosis**

• Fasting insulin concentrations
  ❖ Easy to perform and useful screening test if moderate/severe IR
  ❖ Feed one biscuit hay after 10pm and collect blood next morning
  ❖ Insulin upper limit 30 μU/mL, consider > 20 μU/mL suggestive of IR
  ❖ High normal [glucose] (>5.5mmol/L) also detected in some horses but now not considered useful due to variability/stress
  ❖ Pain and stress associated with acute laminitis markedly elevate resting serum [insulin] – re-evaluate once stable
  ❖ Testing in Australia
  ❖ Vetnostics: protocol in green, $55 (including GST)
  ❖ IDEXX: Serum sample – $74.58 (including GST)

<table>
<thead>
<tr>
<th>Test</th>
<th>Insulin</th>
</tr>
</thead>
</table>
| Suitable Sample: | • SERUM  
  • LH  
  • Sodium fluoride can be used but will give slightly lower values |
| Unsuitable Sample: | • EDTA (negative interference) |
| Minimum Sample Size: | • 2 mL whole blood |
| Turnaround Time: | • Daily |
| Request/Test Included in: | • Request test |
| Comments: | • If suspect insulinoma, collect FL sample for concurrent glucose. |
| Date Updated: | 1/10/2007 |

• Fasting [leptin]
  ❖ >4ng/ml
• [Triglyceride] levels
  ❖ >0.64 mmol/L
• Proxies
  ❖ Single sample predictors of insulin sensitivity using single measurements of plasma [glucose] & [insulin]
  ❖ Inexpensive and easily applied quantitative tools
  ❖ Not recommended at present due to overdiagnosis and variability in [glucose]
### Oral Sugar Test (OST)
- Performed if baseline [insulin], [triglycerides] and [leptin] equivocal
- Protocol 1
  - 0.15ml/kg (75mls per 500kg) PO Karo Light Syrup (IGA/online $8.15 per 470mls)
  - Collect blood sample 60-90mins (75mins average)
  - Positive if [Insulin] >45μU/mL
  - [Glucose] >125mg/dL
- Protocol 2
  - 0.5g/kg or 1g/kg dextrose powder mixed with food (no food overnight)
  - Collect blood sample 60-90mins (75mins average)
  - Positive if [Insulin] >60μU/mL (0.5g/kg) or >87μU/mL (1g/kg)

<table>
<thead>
<tr>
<th>Proxy for</th>
<th>Test name</th>
<th>Acronym</th>
<th>Formula (Gluc mg/dL, Ins μU/mL)</th>
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<tbody>
<tr>
<td>IR</td>
<td>fasting insulin &amp; glucose</td>
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<tr>
<td></td>
<td>homeostasis model assessment for IR</td>
<td>HOMA-IR</td>
<td>[fasting ins x fasting gluc] + 22.5</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>quantitative insulin sensitivity check index</td>
<td>QUICKI</td>
<td>1 + [log fasting ins + log fasting gluc]</td>
</tr>
<tr>
<td></td>
<td>fasting glucose to insulin ratio</td>
<td>FGIR</td>
<td>fasting gluc + fasting ins</td>
</tr>
<tr>
<td></td>
<td>reciprocal inverse square of insulin</td>
<td>RISQI</td>
<td>1 + insulin^{-0.5}</td>
</tr>
<tr>
<td>Pancreatic β cell function</td>
<td>homeostasis model assessment of percentage β cell function</td>
<td>HOMA-B%</td>
<td>[20 x fasting ins] + [fasting gluc – 3.5]</td>
</tr>
<tr>
<td></td>
<td>modified insulin to glucose ratio</td>
<td>MIRG</td>
<td>[800 – 0.3x(ins – 50)^2] + [gluc – 30]</td>
</tr>
<tr>
<td></td>
<td>fasting insulin to glucose ratio</td>
<td>G:I ratio</td>
<td>fasting gluc + fasting ins</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>&gt; 20 μU/mL suggestive</td>
</tr>
<tr>
<td></td>
<td>&gt; 30 μU/mL more definitive</td>
</tr>
<tr>
<td>Glucose</td>
<td>&gt;5.5 mmol/L</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>&gt;0.64 mmol/L</td>
</tr>
<tr>
<td>Leptin</td>
<td>&gt;4ng/ml</td>
</tr>
<tr>
<td>Insulin OST</td>
<td>&gt; 45 μU/mL (Karo Light)</td>
</tr>
<tr>
<td>G:I ratio</td>
<td>&lt; 4.5 Severe</td>
</tr>
<tr>
<td></td>
<td>4.5-10 Compensated</td>
</tr>
<tr>
<td></td>
<td>&gt;10 Normal</td>
</tr>
<tr>
<td>RISQI</td>
<td>&lt; 0.22 Severe IR</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.32 IR</td>
</tr>
<tr>
<td></td>
<td>&gt; 0.32 Normal</td>
</tr>
<tr>
<td>MIRG</td>
<td>&gt; 5.6</td>
</tr>
</tbody>
</table>
• Combined glucose insulin test (CGIT)
  ❖ Dynamic test provides better estimation of insulin sensitivity if mild IR
  ❖ IV catheter placed evening before test to minimise stress confounders
  ❖ Blood collected in fluoride citrate or analysed immediately using a handheld glucometer
    1) Blood collection prior to dextrose
    2) Dextrose 150mg/kg IV bolus as a 50% solution (150ml/500kg) immediately followed by 0.1U/kg regular insulin (0.5ml/500kg)
    3) Blood collection @ 5, 15, 40, 45, 60 mins
  ❖ Small risk of hypoglycaemia – 2 x 60ml syringes 50% dextrose administered if sweating, muscle fasciculations, weakness, [glucose] ≤40mg/dL
  ❖ IR = maintenance of [glucose] above baseline for ≥ 45 mins
  ❖ [Glucose] peak in <15mins (242±17 mg/dL), [insulin] peaks usually seen at 30mins (157±11 IU/mL) in normal horses
• Normal DST unless concurrent PPID
• Normal thyroid hormones – resting T₃ and T₄

Treatment
1) Dietary management
• Remove or restrict pasture access to 1-2h/d
  ❖ Ponies can consume up to 1% of BW as DM within 3 h of pasture turnout, some horses can ingest up to 5%BW per day!
  ❖ Native grass has 50-65% less NSC of improved grasses
  ❖ Seed head, base/roots highest in NSC i.e. cut grass before seeds
  ❖ 3am to 10am – peak production of NSC from photosynthesis in late morning to mid afternoon
  ❖ Low moisture + low nutrient soil = high NSC
  ❖ NSC remains in dry grass until leached by rain
  ❖ Use of grazing muzzles – monitor water intake
  ❖ Restrict turnout when grass is in dynamic growth phase
    ✓ Turning green and growing rapidly in spring
    ✓ First drying out at beginning of summer drought
    ✓ Rapidly growing after heavy summer rain
    ✓ Entering winter dormancy in fall
• Feed hay, eliminate concentrates
  ✓ Programs
    • WEIGH FEED
      • Initially 1.5% ideal BW/d as hay → 1% initial BW/d after 1mth if fails to lose weight OR
      • 1.5% current BW and reduce to 1.5% of ideal BW over several weeks
    ✓ NSC (e.g. sugars, starch, fructans) found within plant cell, structural CHO (e.g. cellulose) make up cell wall → soaking hay in cold water for 30mins will lower sugar content (drain water before feeding)
• Mineral supplementation – Vitamin E 1000U/d
• Complete/bagged forages are available if suitable hay not
2) **Exercise**  
- Promotes weight loss by increasing energy expenditure and is also likely to improve insulin sensitivity  
- Horses with active laminitis cannot be exercised until stable  
- Walking on a lead rope, exercising on a lunge line, turnout in a dirt paddock with no grass, riding encouraged

3) **Medical Therapy**  
- **Indications**  
  - Obesity with weight loss occurring too slowly or short-term whilst management changes are being implemented  
  - [Insulin] >20μU/mL screen and manage, >50-60 μU/mL treat?  
  - Hyperinsulinaemia persists despite attainment of ideal body condition  
- **Levothyroxine sodium** (Eltroxin, Synthroid, Thyro L™)  
  - Synthetic thyroid hormone 0.1mg/kg PO SID  
  - In conjunction with dietary management as feed intake increases in response to drug  
- **Metformin**  
  - Biguanide that inhibits gluconeogenesis and enhances tissue insulin sensitivity  
  - 15mg/kg PO BID, up to 30mg/kg PO BID used  
  - One report of increase in insulin sensitivity (Durham. *EVJ* 2008), but recently reported low bioavailability questions whether dose requires re-evaluation (Hustace. *AJVR* 2009) – new information suggests that it may locally act on the GIT to cause ↓ glucose absorption\(^\text{ACVIM 2012}\)  
  - Expensive, further research required  
- Medication for EMS horses which have are thin in phenotype and not candidates for levothyroxine?  
- **Supplementation not validated:** Magnesium 4-8g/day and Chromium 2.5-5.0mg/day

**Prognosis**  
- EMS is a manageable condition especially if detected prior to onset of laminitis  
- Laminitis risk/recurrence can be minimized in affected horses and more effective treatment implemented  
- Prognosis has improved as new information has become available
**Equine Endocrine Disease**

### History & Clinical Signs
- **Aged >15y**
- **Breed:** pony, Morgan
- **Hypertrichosis (Hirsutism)**
- **Laminitis**
  - Lethargy, hyperhydrdrosis, weight loss, muscle wasting, PU/PD, chronic infections, regional adiposity, infertility
- **Obese BCS ≥7/9

### Test | Interpretation
--- | ---
DST | > 30 pmol/mL (>10 µg/dL)
ACTH (Resting, post TRH 30 mins*) | 7.7pmol/L (>35pg/mL)* 10.3pmol/L (>47pg/ml) Autumn
αMSH | <35pmol/L

### History & Clinical Signs
- **Easy keeper**
- **Breed:** pony, miniature horse, donkey
- **Laminitis**
- **Obese BCS ≥7/9**
- **Cresty neck**
  - Score ≥3/5
  - Mid neck circumference >0.71 ponies
- **Regional adiposity**

### Test | Interpretation
--- | ---
Insulin | > 20 µU/mL suggestive > 30 µU/mL more definitive
Glucose | ≥5.5 mmol/L
Triglyceride | >0.64 mmol/L
Leptin | >4ng/ml
Insulin OST | > 45 µU/mL (Karo Light)
G:I ratio | < 4.5 Severe 4.5-10 Compensated >10 Normal
RISQI | < 0.22 Severe IR < 0.32 IR > 0.32 Normal
MIRG | > 5.6
References
2. Ireland JL et al. EVJ 2012 44:1.
4. Rohrbach et al. ACVIM Proceedings 2010
5. Frank et al. JVIM 2006 20
10. Donaldson MT. JVIM 2005 19:2
15. Chameroy KA et al. EVJ 2010 43:4
To evaluate a horse’s condition, ACO’s and veterinarians use a standard system of checks, developed by Don Henneke, Ph.D., whose illustration and chart originally appeared in the *Equine Veterinary Journal* in 1983. The system involves massaging and scoring six main parts of a horse’s body—neck, withers, shoulder, ribs, loin, and tailhead—on a scale of one to nine for their fat content.

**Henneke Body Condition Scoring System**

Main points checked in Henneke scoring system:
- Neck
- Ribs
- Withers
- Loin
- Shoulder
- Tailhead
<table>
<thead>
<tr>
<th>Condition</th>
<th>Neck</th>
<th>Withers</th>
<th>Shoulder</th>
<th>Ribs</th>
<th>Loin</th>
<th>Tailhead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>Bone structure easily noticeable</td>
<td>Bone structure easily noticeable</td>
<td>Bone structure easily noticeable</td>
<td>Ribs protruding prominently</td>
<td>Spinous processes projecting prominently</td>
<td>Tailhead, pinbones, and hook bones projecting prominently</td>
</tr>
<tr>
<td>Very thin</td>
<td>Bone structure faintly discernible</td>
<td>Bone structure faintly discernible</td>
<td>Bone structure faintly discernible</td>
<td>Ribs prominent</td>
<td>Slight fat covering over base of spinous processes; transverse processes of lumbar vertebrae feel rounded; spinous processes prominent</td>
<td>Tailhead prominent</td>
</tr>
<tr>
<td>Thin</td>
<td>Neck accentuated</td>
<td>Withers accentuated</td>
<td>Shoulder accentuated</td>
<td>Slight fat cover over ribs. Ribs easily discernible</td>
<td>Fat buildup halfway on spinous processes but easily discernible; transverse processes cannot be felt</td>
<td>Tailhead prominent but individual vertebrae cannot be visually identified; hook bones appear rounded but still easily discernible; pin bones not distinguishable</td>
</tr>
<tr>
<td>Moderately thin</td>
<td>Neck not obviously thin</td>
<td>Withers not obviously thin</td>
<td>Shoulder not obviously thin</td>
<td>Faint outline of ribs discernible</td>
<td>Negative crease (peaked appearance) along back</td>
<td>Prominence depends on conformation; fat can be felt; hook bones not discernible</td>
</tr>
<tr>
<td>Moderate</td>
<td>Neck blends smoothly into body</td>
<td>Withers rounded over spinous processes</td>
<td>Shoulder blends smoothly into body</td>
<td>Ribs cannot be visually distinguished but can be easily felt</td>
<td>Back is level</td>
<td>Fat around tailhead feels somewhat soft</td>
</tr>
<tr>
<td>Moderately fleshy</td>
<td>Deposited fat faintly discernible along neck</td>
<td>Deposited fat faintly discernible along withers</td>
<td>Deposited fat faintly discernible behind shoulder</td>
<td>Fat over ribs feels spongy</td>
<td>May have slight positive crease (groove) down back</td>
<td>Fat around tailhead feels soft</td>
</tr>
<tr>
<td>Fleshy</td>
<td>Fat deposited along neck</td>
<td>Fat deposited along withers</td>
<td>Fat deposited behind shoulder</td>
<td>Individual ribs can be felt with pressure but noticeable fat filling between ribs</td>
<td>May have positive crease down back</td>
<td>Fat around tailhead is soft</td>
</tr>
<tr>
<td>Fat</td>
<td>Noticeable thickening of neck</td>
<td>Area along withers filled with fat</td>
<td>Area behind shoulder filled in flush with body</td>
<td>Difficult to feel ribs</td>
<td>Positive crease down back</td>
<td>Fat around tailhead very soft</td>
</tr>
<tr>
<td>Extremely fat</td>
<td>Bulging fat along neck</td>
<td>Bulging fat along withers</td>
<td>Bulging fat behind shoulder</td>
<td>Patchy fat over ribs</td>
<td>Obvious crease down back</td>
<td>Bulging fat around tailhead</td>
</tr>
</tbody>
</table>
Consensus Statements of the American College of Veterinary Internal Medicine (ACVIM) provide the veterinary community with up-to-date information on the pathophysiology, diagnosis, and treatment of clinically important animal diseases. The ACVIM Board of Regents oversees selection of relevant topics, identification of panel members with the expertise to draft the statements, and other aspects of assuring the integrity of the process. The statements are derived from evidence-based medicine whenever possible and the panel offers interpretive comments when such evidence is inadequate or contradictory. A draft is prepared by the panel, followed by solicitation of input by the ACVIM membership, which may be incorporated into the statement. It is then submitted to the Journal of Veterinary Internal Medicine, where it is edited prior to publication. The authors are solely responsible for the content of the statements.

Equine Metabolic Syndrome

N. Frank, R.J. Geor, S.R. Bailey, A.E. Durham, and P.J. Johnson

Key words: Adipokines; Hyperinsulinemia; Insulin resistance; Laminitis; Obesity; Regional adiposity.

The term equine metabolic syndrome (EMS) was first introduced to veterinary medicine in 2002 when Johnson1 proposed that obesity, insulin resistance (IR), and laminitis were components of a clinical syndrome recognized in horses and ponies. The study of EMS is therefore in its infancy, so the following consensus state-

ment reflects our current knowledge of this condition. We anticipate that defining features of the EMS phenotype, approaches to diagnostic testing, and management options will be expanded and updated as further research is performed.

“EMS” was adopted as the name for this condition because of similarities with the metabolic syndrome (MetS) in humans, which is a collection of risk factors assessed to predict the occurrence of coronary artery disease and type 2 diabetes mellitus in people.2 Despite alternative nomenclature having been proposed previously (eg, peripheral Cushing’s syndrome, prelamininetic metabolic syndrome), it was the unanimous decision of the consensus panel to support the use of the term EMS because it has gained wide acceptance and is appropriate when used to define a clinical syndrome unique to equids. The panel proposed that the EMS phenotype for the majority of affected equids should include:

- Increased adiposity in specific locations (regional adiposity) or generally (obesity). Regional adiposity is characterized by expansion of subcutaneous adipose tissues surrounding the nuchal ligament in the neck (cresty neck), development of fat pads close to the tail head, or fat accumulation behind the shoulder or in the prepuce or mammary gland region. Obesity is observed in the majority of cases, but some affected equids have a leaner overall body condition and regional adiposity, and others are normal in appearance. These different phenotype variations require further study.

- IR characterized by hyperinsulinemia or abnormal glycemic and insulminemic responses to oral or IV glucose and/or insulin challenges.

- A predisposition toward laminitis. Clinical or subclinical laminitis that has developed in the absence of recognized causes such as grain overload, colic, colitis, or retained placenta.

Additional components of the EMS phenotype that warrant further consideration include:

- Hypertriglyceridemia or dyslipidemia as a component of EMS in some cases.3–5 Increased very-low-density lipoprotein triglyceride concentrations have also been detected in horses with EMS.5

- Hyperleptinemia resulting from increased secretion of the hormone leptin by adipocytes in response to IR or a state of leptin resistance.6 Leptin is referred to as a satiety factor because it signals the hypothalamus that a state of energy excess exists within adipose tissues.7

- Arterial hypertension4,8 detected in the summer in laminitis-prone ponies, which is recognized as a key component of MetS related to IR in humans.9

- Altered reproductive cycling in mares. Loss of the seasonal anovulatory period10 and prolongation of the interovulatory period11 have been described in obese insulin-resistant mares.

- Increased systemic markers of inflammation in association with obesity.12

History

Contributing factors for obesity should be assessed from the history, including the quantity of feed provided,
size and quality of the pasture, and amount of exercise. Horse owners sometimes refer to affected horses and ponies as “easy keepers” or “good doers” because they require a lower plane of nutrition to maintain body weight than other horses.

Previous episodes of laminitis may be described in the history. Mild episodes of bilateral laminitis may have been mistakenly attributed to sole bruising, arthritis, or foot soreness after trimming or shoeing. If laminitis episodes have been recognized in the past, it should be noted whether the onset of lameness was associated with changes in the abundance or composition of pasture grass, or alterations in grain feeding.

Familial patterns have been recognized for EMS, so relevant information about the horse’s dam and sire should be collected for future reference.

**Clinical Signs**

Clinical signs of EMS include regional adiposity, obesity, bilateral lameness attributable to laminitis, and/or evidence of previous laminitis such as divergent growth rings on the hooves. A cresty neck score has been developed to assess the expansion of adipose tissues within the neck region and scores range from 0 to 5. Scores ≥3 are often detected in horses or ponies with EMS. The description provided for a score of 3 is “Crest enlarged and thickened, so fat is deposited more heavily in middle of the neck than toward poll and withers, giving a mounded appearance. Crest fills cupped hand and begins losing side-to-side flexibility.” Neck circumference can also be measured at the midpoint of the neck with a tape measure. This measurement is taken halfway between the poll and the withers when the neck is in a normal elevated position. The neck circumference-to-height at withers ratio was recently used to predict the development of pasture-associated laminitis in ponies and a cut-off value of >0.71 was established. Body weight should be measured with a scale or weight tape and body condition scoring can be used to assess generalized obesity.

**Pathophysiology**

EMS is a complex disorder for which there are more questions than answers at present. The principal components of EMS are increased adiposity, IR, and laminitis, but this syndrome likely encompasses a much wider spectrum of problems that affect energy metabolism, perturb adipocyte function, promote thrombosis, induce inflammation and oxidant stress, and alter vascular endothelial cell function in affected horses.

**Adiposity**

Environmental (eg, diet, level of physical activity, season) and intrinsic (eg, genetics) factors will affect body fat mass. The mechanisms underlying generalized obesity or regional adiposity in EMS are unknown but chronic overfeeding in association with limited physical activity appears to be a contributing factor. Additionally, horses and ponies with EMS appear to have enhanced metabolic efficiency with respect to the utilization of dietary energy. In this context, it has been suggested that horses and ponies evolutionarily adapted to survival in nutritionally sparse environments are especially predisposed to obesity and IR under modern management conditions in which plentiful feed is available year round. For example, feral and native pony breeds retain strong seasonality with respect to appetite and body condition. Under “feral” conditions these ponies gain weight during the summer months when food is abundant before losing it again during the winter. Seasonal changes in insulin sensitivity also may occur, reflecting alterations in food availability, physical activity, and body condition. Season affected resting serum insulin concentrations in 1 study of obese mares, with higher concentrations detected in December, compared with September, October, and November. In the context of domesticated equids experiencing a chronic state of overnutrition, these seasonal changes in body condition and insulin sensitivity may be replaced by progressive obesity and IR with associated adverse health consequences. More research is required to identify the genetic determinants of metabolic efficiency in horses and the effects of environmental factors such as overnutrition on the expression of these genes.

Adipose tissue is no longer regarded as just an energy storage organ, but an endocrine organ producing many hormones (adipokines or adipocytokines). Adipose tissue dysfunction (with or without obesity) is an important pathophysiologic feature of MetS in humans that may result in IR, systemic inflammation, hypertension, and a prothrombotic status. Adipokines are released from adipocytes and other cells within fat tissues. They include leptin, resistin, adiponectin, visfatin, and apelin as well as inflammatory cytokines released from macrophages and adipocytes such as tumor necrosis factor alpha (TNFα), interleukins 1 (IL-1) and 6 (IL-6), and macrophage chemoattractant protein 1. The inflammatory adipokines may then lead to a self-perpetuating cycle of enhanced adipose tissue inflammation, adipokine synthesis, and secondary acute phase protein synthesis by the liver. Thus obesity in people is characterized by a state of chronic low-grade inflammation.

Few data are available on the pathophysiological effects of obesity or regional adiposity in EMS. Obesity has been associated with reduced insulin sensitivity in horses and ponies, although some obese horses have normal insulin sensitivity. Whether obesity induces IR or the insulin-resistant horse is more predisposed to obesity has not been determined. Further contributory factors to obesity and IR may include altered cortisol metabolism within tissues or leptin resistance, a situation in which tissues fail to respond to leptin.

In humans, mesenteric and omental adipose tissues are thought to play a more important role in the development of type 2 diabetes mellitus than adipose tissues elsewhere because fatty acids and adipokines released from these visceral sites enter the portal circulation and have a more profound effect on hepatic metabolism and insulin clearance. This situation is currently being examined in horses to determine whether adipose tissue from the neck crest or abdomen differs from tissues.
collected from other locations, but results have not yet been published.

**IR**

IR involves defects of insulin signaling such as reduced insulin receptor tyrosine kinase activity and reduced postreceptor phosphorylation steps that impinge on metabolic and vascular effects of insulin. There are two primary theories linking obesity to IR: (1) the down-regulation of insulin signaling pathways induced by adipokines and cytokines produced in adipose tissue; and (2) the accumulation of intracellular lipids in insulin-sensitive tissue such as skeletal muscle (lipotoxicity).

The natural equine diet contains little fat, but excess glucose can be converted into fat via de novo lipogenesis. Fats are used for energy or stored as triglyceride within cells. When the storage capacity of adipose tissues is exceeded, fats are directed toward nonadipose tissues (repartitioning). Skeletal muscle, liver, and pancreatic tissues attempt to utilize fats by increasing β-oxidation, but lipid can accumulate within these tissues and alter normal cellular functions, including insulin signaling.

**Laminitis**

We are limited at present to the knowledge that IR and/or hyperinsulinemia predispose ponies to pasture-associated laminitis and that the condition can be experimentally induced by infusing supraphysiological amounts of insulin IV over 2–3 days. Potential mechanisms relating obesity, hyperinsulinemia, and IR to laminitis are largely extrapolated from studies in other species and include endothelial cell dysfunction within blood vessels of the foot, digital vasoconstriction, impaired glucose uptake by epidermal laminar cells, altered epidermal cell function or mitosis, and matrix metalloproteinase activation by glucose deprivation or reactive oxygen species.

Insulin has vasoregulatory actions and it was the consensus of the panel that this represents a plausible link between IR and laminitis in horses. Vasodilation normally occurs in response to insulin through the increased synthesis of nitric oxide (NO) by endothelial cells. However, insulin may also promote vasoconstriction by stimulating the synthesis of endothelin-1 (ET-1) and activating the sympathetic nervous system. Activation of the insulin receptor stimulates at least two different signaling pathways within the vascular endothelial cell. NO is secreted when the phosphatidylinositol 3-kinase (PI3K) pathway is activated, whereas activation of the mitogen-activated protein kinase (MAPK) pathway leads to the release of ET-1. IR states in humans have been found to involve selective pathway inhibition such that the NO synthetic PI3K pathway is inhibited whereas the MAPK pathway is unaffected and may be overstimulated because of compensatory hyperinsulinemia, which results in increased ET-1 synthesis. Vasoconstriction may therefore be promoted in the insulin-resistant animal as NO production decreases, which might impair the ability of vessels to respond to vascular challenges.

**Epidemiology**

To the panel’s knowledge, there are no published studies on the epidemiology of EMS although there are a few reports on the prevalence of obesity and hyperinsulinemia in populations of ponies and horses. By definition, Welsh, Dartmoor, and Shetland ponies and Morgan Horse, Paso Fino, Arabian, Saddlebred, Spanish Mustang, and warmblood breeds appear to be more susceptible to EMS. However, the panel emphasized that EMS can be prevented through good management practices, so breed susceptibility should be viewed accordingly. EMS also occurs in other light horse breeds, including Quarter Horses and Tennessee Walking Horses, but is rarer in Thoroughbreds and Standardbreds. Miniature horses, donkeys, and draft horses require further study to determine the prevalence of EMS in these groups.

Susceptibility to EMS may be established from before birth, and obesity develops in some horses as soon as they reach maturity. However, most horses with EMS are between 5 and 15 years of age when veterinary or farrier services are first requested because of laminitis.

A seasonal pattern has been identified for laminitis in the United States, with the highest incidence of pasture laminitis around May and June (late spring/early summer). This seasonal rise in laminitis incidence has been attributed to increased nonstructural carbohydrate (NSC) consumption from pasture forage. In the United Kingdom, the highest incidence of pasture laminitis was during the summer (June and July), when sunshine hours and presumably forage NSC content were greatest. This observation provides further circumstantial evidence to suggest a link between grass carbohydrate content and laminitis incidence. Serum insulin concentrations and the reciprocal inverse square of insulin sensitivity measured in ponies predisposed to laminitis suggested a decrease in insulin sensitivity during summer, and this was attributed to changes in pasture carbohydrate composition. Results suggested that aspects of the EMS phenotype in ponies may be latent under conditions of lower or restricted dietary water-soluble carbohydrate (WSC) content, but become apparent when carbohydrate intake increases. Pasture carbohydrate content and climate/seasonal effects are inextricably linked. During periods of high sunshine, when sugars are produced in excess of the energy requirement of the pasture for growth and development, they are converted into storage, or reserve, carbohydrates, such as fructans and starches.

**Diagnosis**

EMS can be diagnosed by obtaining a complete history, performing a physical examination, taking radiographs of the feet, and conducting laboratory tests. Physical examination should include assessment of the horse for evidence of regional adiposity, including adipose tissue expansion within the neck crest, and body condition scoring. Current screening tests for IR focus upon the measurement of glucose and insulin concentra-
tions in single blood samples, although dynamic tests are necessary to properly assess insulin sensitivity. An important goal for the future is the development of a panel of tests to diagnose EMS.

Hyperglycemia is rarely detected in horses with EMS because most animals maintain an effective compensatory insulin secretory response in the face of IR. However, blood glucose concentrations are often toward the higher end of reference range indicating partial loss of glycemic control. If persistent hyperglycemia is detected, a diagnosis of diabetes mellitus should be considered. Type 2 diabetes mellitus occurs in horses and may be more common than thought previously. This diagnosis should be considered when hyperglycemia cannot be attributed to other causes such as stress, recent feeding, or inflammatory processes.

Hyperinsulinemia in the absence of confounding factors such as stress, pain, and a recent feed provides evidence of IR in horses and ponies. However, resting insulin concentrations are not found to be increased in all cases, so dynamic testing provides the most accurate diagnosis of IR. It should also be recognized that reference ranges vary among laboratories, in part because of differences in the assay used. More research is required to determine cut-off values for hyperinsulinemia, but a value of 20 μU/mL is suggested as a general guideline for the upper limit of serum/plasma insulin concentrations in normal horses and ponies.

Sampling conditions are important when diagnosing the chronic IR associated with EMS. Cortisol and epinephrine released as a result of pain or stress lower tissue insulin sensitivity and raise resting glucose and insulin concentrations. Insulin concentrations are likely to be higher in a horse that is currently suffering from laminitis, so testing should be delayed until after the pain and stress of this condition has subsided. Blood samples should be collected after an approximately 6-hour period of feed withholding, ideally between 8:00 and 10:00 AM. These conditions can be achieved by providing not more than 1 flake of low-NSC grass hay per 500 kg bodyweight no later than 10:00 PM the night before sampling. Under these conditions, hyperinsulinemia (> 20 μU/mL) provides evidence of IR. If hyperinsulinemia is not detected, but other components of the EMS phenotype are recognized, a dynamic test of insulin sensitivity should be performed.

Dynamic testing for evaluation of insulin sensitivity is recommended because tissue insensitivity to insulin may only be revealed when glycemic control is challenged by inducing hyperglycemia. A number of tests can be used for this purpose, and an ideal test for diagnosing IR in horses has not been established to date. Testing should be conducted under the same conditions as blood sampling for resting glucose and insulin measurements. Horses must be tested after the pain and stress of laminitis has subsided, and after an approximately 6-hour fast to limit confounding effects of recent feed consumption. Oral or IV glucose tolerance tests can be performed to raise blood glucose and insulin concentrations and determine the height and width of the resulting curve. Area under the curve values provide the best measure of glucose tolerance, although the peak concentration and time taken for concentrations to return to baseline can also be evaluated. The combined glucose-insulin test (CGIT) developed by Eiler et al can also be used to diagnose IR in horses. Insulin is injected immediately after dextrose to lower blood glucose concentrations. Advantages of the CGIT include the shorter time required for testing and information gained about both the glycemic and insulinemic responses. A CGIT is performed by first obtaining a preinjection blood sample for baseline glucose and insulin measurements, and then injecting 150 mg/kg body weight (bwt) 50% dextrose solution IV, immediately followed by 0.10 U/kg bwt regular insulin IV. These dosages are equivalent to 150 mL of 500 mg/mL (50%) dextrose and 0.50 mL of 100 U/mL insulin for a horse weighing 500 kg. Insulin should be drawn into a tuberculin syringe and then transferred into a larger syringe containing 1.5-mL sterile saline (0.9% NaCl) before injection. Blood glucose concentrations are measured at 1, 5, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135, and 150 minutes postinfusion.

When the CGIT is performed in healthy animals, blood glucose concentrations return to below the baseline value by 45 minutes, so preliminary results are available within 1 hour if a glucometer is used. Blood collected at 0 and 45 minutes is submitted for insulin assay and this allows the insulin response to be evaluated. Horses with insulin concentrations > 100 μU/mL at 45 minutes are secreting more insulin than normal and/or clearing the hormone from the circulation at a slower rate. This is interpreted as an indication of IR. The test can be abbreviated to 60 minutes when used in the field, but it is advisable to complete all of the measurements so that the horse’s complete response can be recorded for future comparison. Hypoglycemia is a potential complication of testing, although this is rarely encountered in the patients selected for testing. If clinical signs of hypoglycemia (sweating, weakness, and muscle fasciculation) are recognized or if blood glucose concentrations fall below 40 mg/dL (2.2 mmol/L), administer 60 mL of 50% dextrose IV and repeat as necessary.

In addition to glucose, it has been found that feeding some other carbohydrates to ponies induces an exaggerated insulin response in IR individuals. These carbohydrates include inulin, a type of fructan carbohydrate. Furthermore, the administration of dexamethasone also elicits this exaggerated insulin response. These observations may have implications for the likely causes of hyperinsulinemia in horses or ponies with EMS that are grazing on pasture, putting them at risk of laminitis. These tests require further validation.

Future directions for diagnostic testing include the development of a test panel consisting of assays that can be performed on a single blood sample. Such a panel might further include the adipokines leptin, adiponectin, and resistin, lipids such as triglyceride and nonesterified fatty acids, fructosamine as a reflection of blood glucose concentrations, and measures of systemic inflammation including TNF-α, IL-1, IL-6, C-reactive protein, serum amyloid A, and plasminogen activator inhibitor-1.
blood cell count, PCV, iron concentration, and plasma gamma glutamyl transferase (GGT) activity might also be included on the panel. Anemia is sometimes detected in EMS horses, and some affected horses have shown elevated GGT activity that has corresponded with hepatic lipidosis, detected in biopsy and necropsy specimens. Pancreatic insulin secretion may be assessed by measuring serum connecting peptide (C-peptide) concentrations. This peptide is released in equimolar amounts with insulin, but is not cleared from the blood by the liver. Approximately 60% of the insulin secreted by the pancreas is extracted from the portal blood by the liver in healthy humans, so hyperinsulinemia can develop as a result of reduced insulin clearance and/or increased pancreatic secretion. Serum C-peptide concentrations can indicate the relative contributions of these processes. Recent research suggests that reduced insulin clearance significantly contributes to hyperinsulinemia in horses with EMS, so the C-peptide-to-insulin ratio may be useful to further characterize the hyperinsulinemia detected in equids.

Differentiating EMS from Pituitary Pars Intermedia Dysfunction (PPID; Equine Cushing’s Disease)

Regional adiposity and laminitis are clinical signs of PPID as well as EMS, so both endocrine disorders should be considered when these problems are detected. EMS may be differentiated from PPID by:

- Age of onset: The EMS phenotype is generally first recognized in younger horses, whereas PPID is more common in older horses; although these disorders may coexist.
- Further clinical signs suggestive of PPID, but not EMS, including delayed or failed shedding of the winter haircoat, hirsutism, excessive sweating, polyuria/polydipsia, and skeletal muscle atrophy.
- Positive diagnostic test results for PPID: For example, detection of an increased plasma adrenocorticotropic hormone concentration in the absence of confounding factors such as pain and stress, and outside of the late summer/autumn period when false positive results occur in healthy horses and ponies.

Reduced glucose tolerance indicative of IR has also been detected in horses with PPID. However, it was the consensus of the panel that normal insulin sensitivity is more common in horses with PPID, which suggests that the relationship between these conditions is complex. Discussion of this subject generated several questions that require further research, including:

1. Does IR only accompany PPID when the animal was insulin resistant before pituitary dysfunction developed? If this is the case, PPID may exacerbate IR, but not be the cause of the problem.
2. If PPID causes IR in some horses, but not others, is this a particular manifestation of the disorder? Are specific hormones responsible for IR in these PPID patients?
3. Are the effects of PPID on insulin sensitivity dependent upon the stage of the condition?
4. Does EMS represent a risk factor for PPID?

The consensus panel recognized that some equids with EMS subsequently develop PPID, so both conditions can occur concurrently. Anecdotal reports suggest that horses and ponies with EMS are predisposed to PPID and pituitary dysfunction develops at a younger age in affected animals. Further research is required in this area, but the panel recommends that equids with EMS be closely monitored for clinical signs of PPID and undergo regular testing for the condition. If PPID is causing and/or exacerbating IR, treatment should improve insulin sensitivity. Pergolide is recommended for the treatment of PPID in equids.

Dietary Management

Dietary management of EMS involves reducing the amount of energy provided in the diet to induce weight loss if the horse or pony is obese and lowering the NSC content of the diet to reduce glycemic and insulimic responses to meals. Reducing the digestible energy (DE) content of the diet is an important factor in moderating obesity as a contributory factor to EMS. Limiting or eliminating pasture grass from the diet is a key component of this approach because pasture grazing provides DE that cannot be quantified. Obese horses and ponies should be provided a forage diet with mineral/vitamin supplementation. Hay with low NSC content should be selected, which can be determined by submitting a sample for analysis or by purchasing forage with a declared nutrient analysis. Simple sugars, starches, and fructans are NSC, whereas cellulose and hemicelluloses are structural carbohydrates. It was thought previously that fructans undergo minimal hydrolysis until they reach the large intestine of the horse, so they would be less likely to contribute to the glycemic response after a meal. However, there is some evidence indicating that there may be appreciable microbial and acid hydrolysis of fructans before they reach the equine large intestine. Furthermore, insulin-resistant ponies exhibit an insulin response to dietary fructans. It is therefore recommended that NSC be calculated by adding starch and WSC percentages together, and this value should ideally fall below 10% of dry matter when feeding horses or ponies with EMS. Hay can be soaked in cold water for 60 minutes to lower the WSC content if the amount of NSC exceeds 10%. However, a recent study demonstrated that results vary markedly among different hay samples, so this strategy cannot be relied upon to completely address the problem of high WSC concentrations in the hay that is being fed to a horse or pony with EMS.

Weight loss should be induced in obese horses by restricting the total number of calories consumed and by increasing the individual’s level of physical activity. In horses that are being overfed, removal of all concentrates
from the diet is sometimes sufficient to induce weight loss. An obese horse should be placed on a diet consisting of hay fed in an amount equivalent to 1.5% of ideal body weight (1.5 lb hay per 100 lb bwt). Hay should be weighed on scales to ensure that correct amounts are fed. If an obese horse or pony fails to lose weight after hay has been fed at an amount equivalent to 1.5% of ideal body weight for 30 days, this amount should be lowered to 1%. However, amounts should not fall below this minimum of 1% and it should be noted that severe calorie restriction may lead to worsening of IR, hyperlipemia, and unacceptable stereotypical behaviors.

Pasture access should be eliminated until insulin sensitivity has improved because carbohydrates consumed on pasture can trigger gastrointestinal events that lead to laminitis in susceptible horses.46 Mildly affected horses can return to pasture once obesity and IR have been addressed, but care must be taken to restrict pasture access when the grass is going through dynamic phases, such as rapid growth in the spring or preparation for cold weather in the fall. Measurement of pasture grass NSC content at different times of the day has revealed that grazing in the early morning is likely to be safer for horses with IR, except after a hard frost when grasses accumulate WSC.47 Other risk factors for high fructan content include regular cutting, cool, and bright conditions and predominance of certain grass species such as ryegrass.32,48 Strategies for limiting grass consumption include short (<1 hour) turnover periods (or hand-grazing), confinement in a small paddock, round pen, or area enclosed with electric fence, or use of a grazing muzzle. Horses and ponies with EMS can have rapid rates of grass intake, so >1–2 hours grazing may be excessive for these animals.32 Unfortunately, severely insulin-resistant horses that suffer from recurrent laminitis must be kept off pasture permanently. These patients should be housed in dirt paddocks so that they are able to exercise once hoof structures have stabilized. Forage only diets will not provide adequate protein, minerals, or vitamins. Supplementing the forage diet with a low-calorie commercial ration balancer product that contains sources of high-quality protein and a mixture of vitamins and minerals to balance the low vitamin E, vitamin A, copper, zinc, selenium, and other minerals typically found in mature grass hays is therefore recommended. These products are designed to be fed in small quantities (eg, 0.5–1.0 kg total per day).

Insulin-resistant horses with a thinner overall body condition are challenging to manage from a dietary standpoint because hay alone may not meet energy requirements. Commercial low-NSC feeds are available for use in these situations in which digestible fibers (beet pulp or soya hulls) and/or vegetable oils are included in place of starch-rich ingredients. The energy density (ie, DE per kg) of these feeds is variable depending on composition, so energy requirements and the severity of IR must be taken into account before feed selection. It is also better to divide the daily ration into multiple small meals and to feed hay beforehand as this may slow the rate of feed intake and gastric emptying and minimize postfeeding increases in the circulating concentrations of both glucose and insulin. Alternatively, the energy density of the ration can be increased by feeding soaked beet pulp shreds (nonmolassed) or vegetable oil. The latter can be mixed with beet pulp or with hay cubes that have been soaked in water. Corn and soy oils are commonly used in equine rations; 1 standard cup (~225 mL or 210 g) of vegetable oil provides 1.7 Mcal (7.1 MJ) of DE. Depending on energy requirements, 1/2 to 1 cup of oil can be fed once or twice daily. Smaller amounts (eg, 1/4 cup once daily) should initially be fed, with a gradual increase over a 7- to 10-day period. With all of these strategies, the goal is to lower the glycemic and insulimic response to the meal, which is the degree to which blood glucose and insulin concentrations rise in response to the feed. Further information regarding the dietary management of obesity and IR in equids is provided in a recent review.49

Physical Activity

Regular physical exercise is an effective therapeutic intervention to improve insulin sensitivity in obese insulin-resistant people. An exercise prescription of approximately 200 minutes per week of moderate intensity exercise results in a sustained increase in insulin sensitivity50,51 and improvements in other risk factors (eg, lipid profile) that are criteria for MetS.52 Furthermore, improvements in insulin sensitivity associated with physical activity can occur in the absence of weight loss or change in fat distribution.53 Therefore, subject to the status of foot pain and structural damage, an increase in physical activity is recommended for equids with EMS in order to promote weight loss and improve insulin sensitivity.54,55 More research is required to determine an optimal exercise prescription for management of EMS, but a general recommendation is to start with 2–3 exercise sessions per week (riding and/or longeing), 20–30 minutes per session. Subsequently, there should be a gradual increase in the intensity and duration of exercise, for example, building to 5 sessions per week.

Medical Management

Most horses and ponies with EMS can be effectively managed by controlling the horse’s diet, instituting an exercise program, and limiting or eliminating access to pasture. Many studies have revealed that IR in human subjects is controlled most effectively by changes in lifestyle and diet although these strategies may fail due to lack of self-discipline.56 Similarly, compliance of the owner/manager is critical to the success of management changes designed to alleviate risk factors for laminitis in EMS.

Pharmaceutical products used to treat IR and type 2 diabetes mellitus in humans primarily include insulin sensitizers comprising metformin (a biguanide) and thiazolidinediones (pioglitazone and rosiglitazone); and insulin secretagogues comprising sulphonylureas (glyburide [glibenclamide], glipizide and glimepiride), repaglinide (a benzoic acid derivative), and nateglinide (a phenylalanine derivative).57 In horses, only levomethoroxine sodium and metformin have thus far received any attention in the context of medical management of IR and EMS.
**Levothyroxine Sodium**

Weight loss can be induced and insulin sensitivity improved by administering levothyroxine sodium to horses.\(^5\) Levothyroxine sodium is given to horses and larger (> 350 kg) ponies at a dosage of 48 mg/day in the feed for 3–6 months at the same time that diet and exercise interventions are initiated. Smaller ponies and Miniature horses are given 24 mg levothyroxine sodium per day for the same time period. Treated horses should be weaned off levothyroxine sodium once ideal body weight has been attained by reducing the dosage to 24 mg/day for 2 weeks and then 12 mg/day for 2 weeks.

Serum tT4 concentrations often range between 40 and 100 ng/mL in treated horses, indicating that levothyroxine sodium is being given at a supraphysiological dosage. However, clinical signs of hyperthyroidism such as emaciation, sweating, tachycardia, or tachypnea have not been observed in treated horses.\(^5\) \(^5\) \(^6\) \(^1\) Benefits of treating horses with levothyroxine at lower dosages for longer periods have not been evaluated scientifically.

**Metformin**

Positive responses to metformin have been reported in hyperinsulinemic horses and ponies at a dosage of 15 mg/kg twice daily PO.\(^6\) Insulin sensitivity estimated by proxy measures improved in treated animals, without the adverse effect of hypoglycemia. Metformin is a biguanide drug that enhances the action of insulin within tissues at the postreceptor level most likely by promoting AMP-dependent protein kinase.\(^6\) Inhibition of gluconeogenesis and glycogenolysis within the liver appears to be its main mode of action along with many other insulin- and noninsulin-related effects.\(^6\) Results of this first study look promising, but safety studies have not been performed to date in horses, so this must be considered before the drug is prescribed long term. Results of recent pharmacokinetic studies indicate that oral bioavailability of metformin is lower in horses than humans.\(^5\) \(^5\) \(^6\) \(^6\) Efficacy might therefore be improved by further investigation of appropriate dosing schedules.

**Supplements and Nutraceuticals**

Chromium, magnesium, cinnamon, and chasteberry (Vitex agnus-castus) are commonly recommended for the management of EMS. It was the consensus of the panel that there is insufficient scientific evidence to support the use of these supplements at this time and that results of controlled studies should be examined before these products are recommended.

**Footnotes**


\(^f\) Measured by Coat-A-Count insulin radioimmunoassay (Siemens Medical Solutions Diagnostics, Los Angeles, CA), Immulite insulin solid-phase chemiluminescent assay (Siemens Medical Solutions Diagnostics), or DSL-1600 insulin radioimmunoassay (Diagnostic Systems Laboratory Inc, Webster, TX)


**References**