2025 Endocrine Updates

Clinical Research & SGLT2 inhibitors

Jamie Pribyl, DVM

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IDPPID

Pituitary Pars Intermedia Dysfunction and Insulin Dysregulation in Equids

Time-period	Total Tested**	Horses with endocrine disease	PPID+	ID+	PPID+/ ID+	PPID+/ ID-	PPID-/ ID+	PPID-/ ID-
2013-2015	2,994	2,340	1,176	1,164	571	605	593	1,225
2016-2020*	22,538	16,550	10,336	12,774	6,559	3,776	6,215	5,988
				High laminitis risk[1]	High laminitis risk[1]		High laminitis risk[1]	

** Horses tested with complete information

1. Equine Endocrinology Group. 2024 Recommendations for the diagnosis and treatment of equine metabolic syndrome (EMS)

Horses that were PPID+/ID+ were >3X higher risk of laminitis than PPID+/ID- horses.

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Foundation

- Only test horses with history and clinical signs ***consistent*** with pituitary pars intermedia dysfunction (PPID)
  - Does that "literally" apply to horses suspected of insulin dysregulation (ID?
- To establish a diagnosis of PPID *and at recheck*, use a ***combination*** of:
  - History from owner
  - Clinical signs
  - Laboratory results
- ***Always evaluate:***
  - adrenocorticotropic hormone (ACTH)
  - *insulin* and glucose

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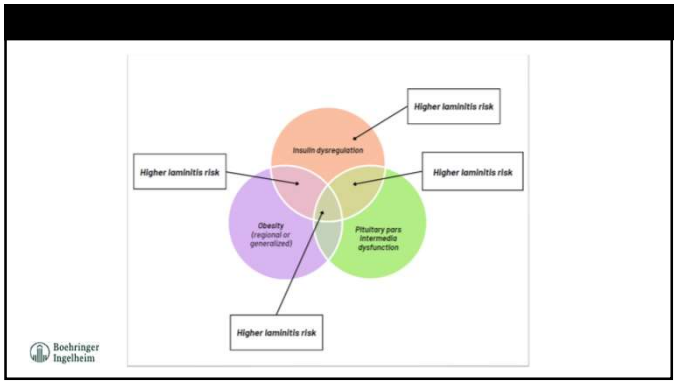
Higher laminitis risk
Insulin dysregulation
Higher laminitis risk
Higher laminitis risk
Obesity (regional or generalized)
Pituitary pars intermedia dysfunction
Higher laminitis risk
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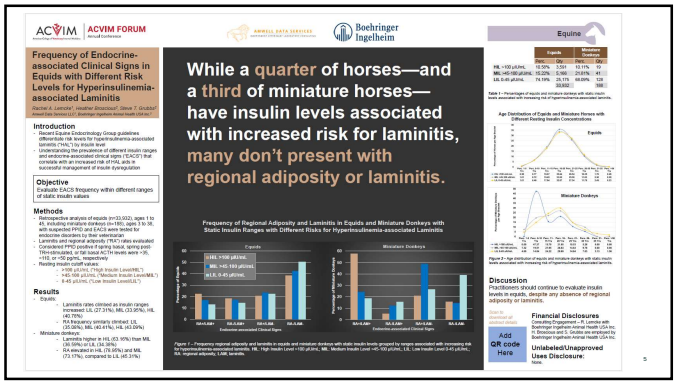
ACVIM FORUM
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Frequency of Endocrine-associated Clinical Signs in Equids with Different Risk Levels for Hyperinsulinemia-associated Laminitis
Introduction
Objective
Evaluate EACS frequency within different ranges of static insulin values
Methods
Results
While a quarter of horses—and a third of miniature horses—have insulin levels associated with increased risk for laminitis, many don't present with regional adiposity or laminitis.
Frequency of Regional Adiposity and Laminitis in Equids and Miniature Donkeys with Static Insulin Ranges with Different Risks for Hyperinsulinemia-associated Laminitis
Equids
Miniature Donkeys
Discussion
Practitioners should continue to evaluate insulin levels in equids, despite any absence of regional adiposity or laminitis.
Financial Disclosures
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Add QR code Here

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2025 idPPID
Research Update #2
Frequency of Endocrine-associated Clinical Signs in Equids with Different Risk Levels for Hyperinsulinemia-associated Laminitis
Rachel A. Lemcke[1], Heather Broscious[1], Steve T. Grubbs[2]
Amwell Data Services LLC[1], Boehringer Ingelheim Animal Health USA Inc.[2]
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Frequency of Endocrine-associated Clinical Signs in Equids with Different Risk Levels for Hyperinsulinemia-associated Laminitis

Main findings:

While a quarter of horses—and a third of miniature horses—have insulin levels associated with increased risk for laminitis, many don't present with regional adiposity or laminitis.

Why does this matter?

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Frequency of Endocrine-associated Clinical Signs in Equids with Different Risk Levels for Hyperinsulinemia-associated Laminitis

Research Objective: Evaluate frequency of endocrine-associated clinical signs within different ranges of static (resting) insulin values

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Frequency of Endocrine-associated Clinical Signs in Equids with Different Risk Levels for Hyperinsulinemia-associated Laminitis

- Two clinical signs evaluated:
  - Laminitis (chronic and acute)
  - Regional adiposity
- Resting insulin cutoff values:
  - **>100** µIU/mL ("High Insulin Level/**HIL**")
  - **>45-100** µIU/mL ("Medium Insulin Level/**MIL**")
  - **0-45** µIU/mL ("Low Insulin Level/**LIL**")

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Frequency of Endocrine-associated Clinical Signs in Equids with Different Risk Levels for Hyperinsulinemia-associated Laminitis

	Equids		Miniature Donkeys	
	Perc.	Qty	Perc.	Qty
HIL >100 µIU/mL	10.58%	3,591	10.11%	19
MIL >45-100 µIU/mL	15.22%	5,166	21.81%	41
★ **LIL** 0-45 µIU/mL	74.19%	25,175	68.09%	128
		33,932		188

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Frequency of Endocrine-associated Clinical Signs in Equids with Different Risk Levels for Hyperinsulinemia-associated Laminitis

- **Equids results:**
  - Laminitis rates climbed as insulin ranges increased:
    LIL (27.31%), MIL (33.95%), HIL (40.78%)
  - RA frequency similarly climbed:
    LIL (35.08%), MIL (40.41%), HIL (43.09%)
- **Miniature donkey results:**
  - Laminitis higher in HIL (63.16%) than MIL (36.59%) or LIL (34.38%)
  - RA elevated in HIL (78.95%) and MIL (73.17%), compared to LIL (45.31%)

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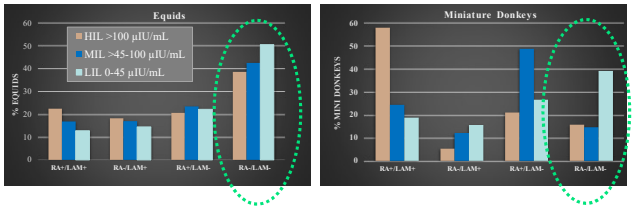
Frequency of Endocrine-associated Clinical Signs in Equids with Different Risk Levels for Hyperinsulinemia-associated Laminitis

Frequency of Regional Adiposity and Laminitis in Equids and Miniature Donkeys with Static Insulin Ranges with Different Risks for Hyperinsulinemia-associated Laminitis



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Frequency of Endocrine-associated Clinical Signs in Equids with Different Risk Levels for Hyperinsulinemia-associated Laminitis

Take Home Message:

Practitioners should continue to evaluate insulin levels in equids, **despite any absence of regional adiposity or laminitis.**

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Received: 30 August 2019 | Accepted: 14 February 2020
DOI: 10.1111/jvim.15747

STANDARD ARTICLE

Journal of Veterinary Internal Medicine ACVIM

Blood glucose and insulin concentrations after alpha-2-agonists administration in horses with and without insulin dysregulation

Janice E. Kritchevsky[1] | Genevieve S. Muir[2] | Dakota H. Z. Leschke[2] | Jack K. Hodgson[2] | Emily K. Hess[1] | Francois-Rene Bertin[2]

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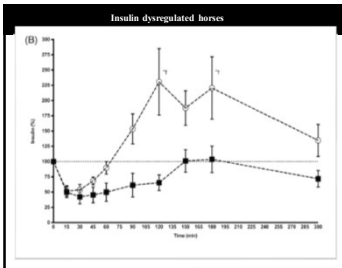
Insulin dysregulated horses



Control horses

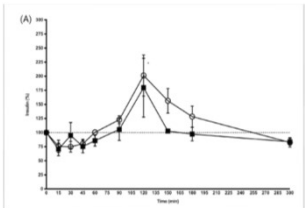


FIGURE 2 Mean (± SD) insulin concentration (percentage of baseline) after IV administration of xylazine hydrochloride (open circles) and detomidine hydrochloride (black squares) in 7 control horses (solid line, panel A) and 7 insulin dysregulated horses (dashed line, panel B). *P < .05 versus baseline; †P < .05 xylazine versus detomidine

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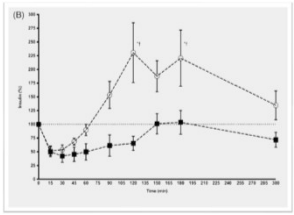
Conclusion



Administration of alpha-2-agonists resulted in an initial decrease in blood insulin in both control and ID horses; followed by a marked increase in insulin secretion with xylazine

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Questions

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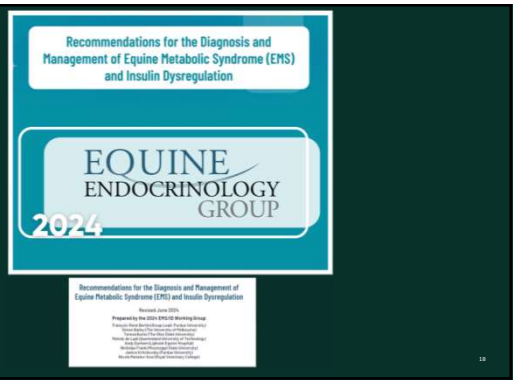

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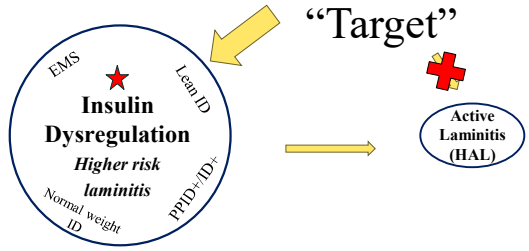
Recognition
"Target"



Active Laminitis (HAL)

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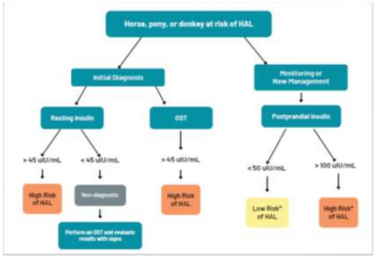
The guiding principle for interpretation of insulin results:

The risk of HAL increases as insulin concentrations increase



Evaluate adiponectin!

micro units per milliliter (uIU/mL)

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*Between 50 and 100 µIU/mL, the risk of laminitis has not been entirely established

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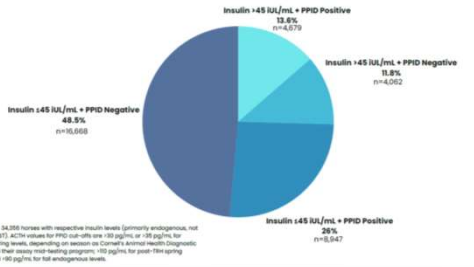
Frequency of Hyperinsulinemia (>45 iUL/mL)and PPID in IDPPID Program 2016-2023



Data represents 34,356 horses with respective insulin levels (primarily endogenous, not dynamic with OST). ACTH values for PPID cut-offs are >30 pg/mL or >35 pg/mL for endogenous spring levels, depending on season as Cornell's Animal Health Diagnostic Center modified their assay mid-testing program; >10 pg/mL for post-TRH spring stimulation; and >80 pg/mL for fall endogenous levels.

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Breed	Some breeds have an increased risk of developing ID. At-risk breeds include pony breeds, Iberic breeds (Andalusians), gaited breeds (Saddlebreds, Paso Finos), Morgans, Miniature horses, Arabian horses, and Warmbloods.
Genetics	Some genes have been associated with the development of ID; however, the condition is a complex genetic disease (involving multiple genes) and the contribution of currently identified genes seems limited compared to environmental factors. This means that ID is therefore a manageable disease in most affected cases.
Age	Age has been identified as a risk factor for ID; therefore, it is recommended to include yearly testing of at-risk horses as they get older than 5 years of age.
Obesity	Obesity is considered an exacerbating factor of ID and associations between obesity (regional and general) and ID have been inconsistent; therefore, testing should not be limited to obese horses.
Diet	A diet high in NSC is a risk factor for the development of ID regardless of genetic predispositions; any horse on an NSC-rich diet is at risk of developing ID and HAL.
PPID	PPID is a risk factor for the development of ID; however, the specific link between the two conditions is unclear. Investigation of ID in horses diagnosed with PPID is strongly recommended.

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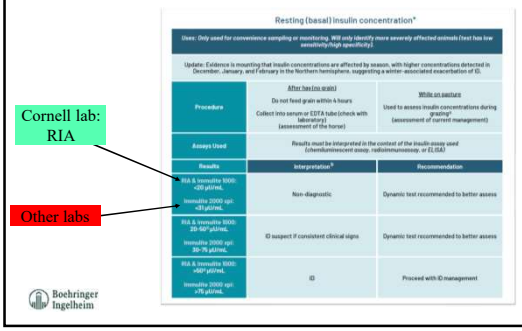

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- **Post-grazing insulin concentrations:**
  - Postprandial insulin level assesses the insulinemic effects of what the horse is eating
    - Therefore, assessing laminitis risk of the current diet
  - **Advantage**: reflects actual laminitis risk of horse consuming current diet
  - Collect blood sample prior to turn-out, then 2 hours post taken off pasture
  - Used for monitoring purposes, assessing current diet (pasture)
  - Insulin values likely vary depending time of year and pasture changes

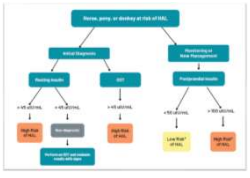

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Table 3 – Recommended dynamic testing for a diagnosis of ID

	Hyperinsulinemia	*Tissue insulin resistance*
	Oral Sugar Test (OST)	**Insulin Tolerance Test (ITT)**
Procedure	**Fast 3 – 6 hours** [A]Administer 0.15 mL/kg corn syrup orally via dose syringe Collect blood at 60 and/or 90 minutes Measure insulin and glucose	**Do not fast** Collect blood at time 0 minutes Administer 0.10 IU/kg regular (soluble) insulin Collect blood at 10 minutes Measure glucose Feed hay and small amount of grain after last sample
Interpretation	>45 µIU/mL are consistent with post-prandial hyperinsulinemia	< 50% decrease in blood glucose concentrations from baseline is consistent with insulin resistance

Note that hypoglycemia is a risk associated with the ITT and try to minimize stress prior to testing.
A higher dose of 0.45 mL/kg corn syrup can also be used for the OST, and insulin concentrations >85 µIU/mL (RIA) or >63 µIU/mL (Immulite 2000 xpi) are consistent with post-prandial hyperinsulinemia.

NOT a focus at this time

[A] Karo Light; ACH Food Companies, Inc, Cordova, TN.

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Medical treatments in research phases

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

- Used when horses are affected by laminitis and severe ID and:
  - The owner has sufficient resources to pay for an expensive medical treatment
- Drugs in this group act by inhibiting the reuptake of glucose from the glomerular filtrate (kidney)
  - Excess glucose is excreted in the urine as a result
- Blood glucose concentrations decrease in response to treatment
  - The amount of insulin needed to maintain euglycemia decreases
    - **Insulin levels decrease…**

1. Canagliflozin
2. Ertugliflozin
3. Velagliflozin

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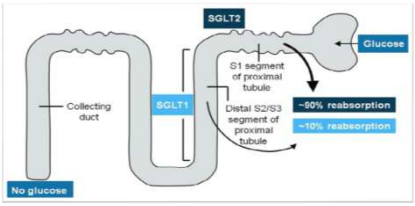
How SGLT2 Inhibitors Work (sodium-glucose cotransporter-2 inhibitors)

- SGLT2 is a protein in humans that facilitates glucose reabsorption in the kidney
  - SGLT2 inhibitors block the reabsorption of glucose in the kidney
  - Increase glucose excretion
  - Lower blood glucose levels



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SGLT2 Inhibitors

No FDA approved products for the horse

Human Products:

- canagliflozin
  - 0.4 mg/kg to **0.6 mg/kg** once daily (0.5 mg/kg SID)
  - 100 mg and 300 mg tablets
- ertugliflozin
  - 0.05 mg/kg SID
  - 5 mg and 15 mg tablets

Other Products:

- Compounded ertugliflozin
  - 0.05 mg/kg SID
  - Multiple formulations available

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SGLT2 Inhibitors

Possible side effects to monitor for horses:

- Elevated triglycerides
- Increased/marked lipemia
- Liver enzymes???

Human products: $500 – 900/month

	Horse 1	
Week	Dosage	Results
0	N/A	I:139
2	0.5 mg/kg	I: 36 T: 561
6	0.25 mg/kg	I: 67 T: 169
10	0.5 mg/kg	I: 29 T: 128
18	0.5 mg/kg	I: 20 T: 24
28	0.5 mg/kg	I: 36 T: 57
36	0.5 mg/kg	T: 26 T:89

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Continuous Monitoring!!

until we understand more…….

- Lipid mobilization is stimulated in many (MOST) horses treated with SGLT2 inhibitors
  - Elevated triglycerides typically develop
- Horses with elevated triglycerides prior to treatment should not be treated with these drugs
- Humans: hypoglycemia, urinary tract infections, others

- **Recommendations in horses:**
  - Monitor *closely* while being treated:
    - Appetite, overall health
    - Insulin levels
    - Glucose levels
    - Triglyceride levels
    - Liver enzymes

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SGLT2 Inhibitors

Continuous monitoring…..
in horses until we understand more

Recommendations in horses:

- Monitor closely while being treated:
  - Appetite, overall health
  - Insulin levels
  - Glucose levels
  - Triglyceride levels
  - Liver enzymes
    - Monitoring suggestions: baseline, 2wks, 1mo, monthly?
  - PROPER DIET ★

SGLT2i are **NOT** a substitute for an improper diet

Proper diet + SGLT2i = BEST outcome

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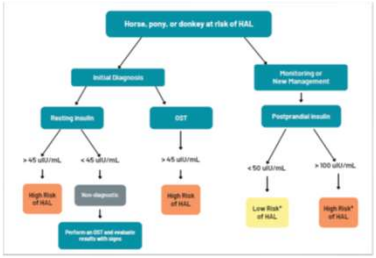
The guiding principle for interpretation of insulin results:

The risk of HAL increases as insulin concentrations increase



micro units per milliliter (uIU/mL)

*Between 50 and 100 µIU/mL, the risk of laminitis has not been entirely established

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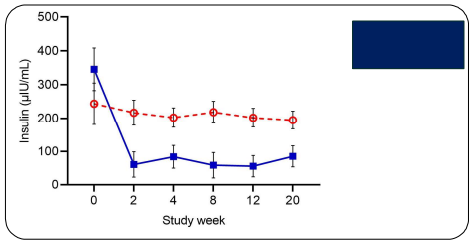
SGLT2 inhibitor (SGLT2i) Equine Formulation



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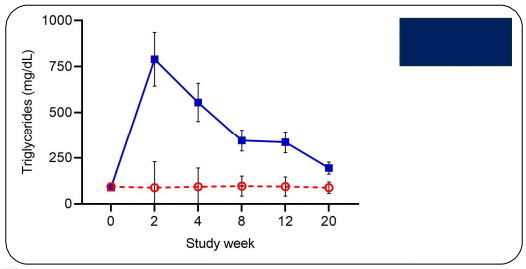
SGLT2 inhibitor (SGLT2i) Equine Formulation



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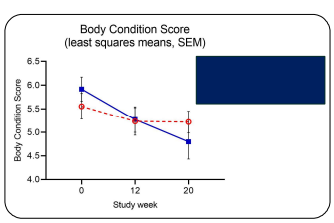
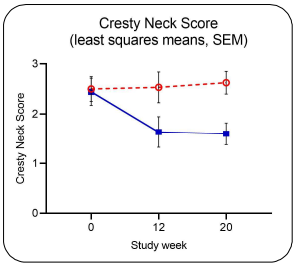
SGLT2 inhibitor (SGLT2i) Equine Formulation





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SGLT2i: Canagliflozin

	Horse 1	
Week	Dosage	Results
0	N/A	I:139
2	0.5 mg/kg	I: 36 T: 561
6	0.25 mg/kg	I: 67 T: 169
10	0.5 mg/kg	I: 29 T: 128
18	0.5 mg/kg	I: 20 T: 24
28	0.5 mg/kg	I: 36 T: 57
36	0.5 mg/kg	T: 26 T:89

	Horse 3	
Week	Dosage	Results
0	N/A	I: 239 T: 155
2	0.5 mg/kg	I: 55 T: 155
6	0.5 mg/kg	I:85 T:93
10	0.5 mg/kg	I:44 T:78
18	0.5 mg/kg	I:45 T:97
28	0.5 mg/kg	I:59 T:91

	Horse 2	
Week	Dosage	Results
0	N/A	I: 354
2	0.5 mg/kg	I: 42 T: 24
6	0.5 mg/kg	I: 87 T: 45
10	0.5 mg/kg	I:131 T:182
18	0.5 mg/kg	I:333* T:186
28	0.5 mg/kg	I:32 T:150
36	0.5 mg/kg	I:36

	Horse 4	
Week	Dosage	Results
0	N/A	I: 333 T:105
2	0.5 mg/kg	I: 53 T: 188
6	0.5 mg/kg	I: 17 T: 151
10	0.5 mg/kg	I:31 T:506
18	0.5 mg/kg	I:20 T:233
26		
36		

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	Horse 5	
Week	Dosage	Results
0	N/A	I: 301 T:33
2	0.5 mg/kg	I: 38 T: 331
6	0.5 mg/kg	I: 23 T: 273
10	0.5 mg/kg	I:58 T:90
18	0.5 mg/kg	I:243* T:52
26		
36		

* carrots…….by owner

- When laboratory results do not make sense (at recheck)
  - Horse receiving/consuming meds/missed doses?
  - Ask questions – politely push for "honest" answer
  - Recheck diet
    - Changes??
    - Carrots/treats??
    - Hay change/turnout?

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Horse 6		
Week	Dosage	Results
0	N/A	I: 239 T: 155
2	0.5 mg/kg	I: 55 T: 155
6	0.5 mg/kg	I:85 T:93
10	0.5 mg/kg	I:44 T:78
18	0.5 mg/kg	I:45 T:97
28	0.5 mg/kg	I:59 T:91

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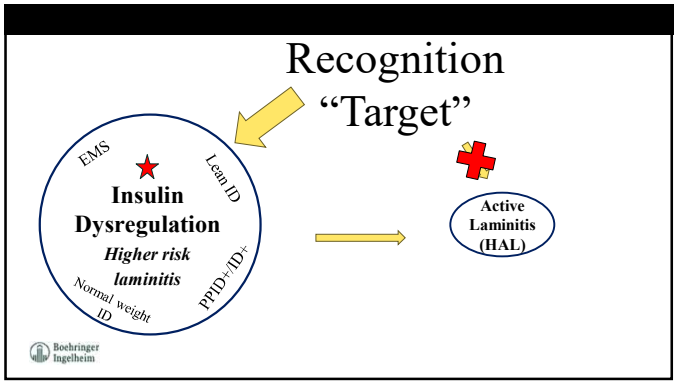

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Adipokines
Leptin & adiponectin

Steven T. Grubbs, DVM, PhD, DACVIM

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Adipokines (leptin & adiponectin)

- Proteins derived from adipose tissue that have local and systemic effects, are important factors in the pathophysiology of obesity and its related conditions
- Much of the information regarding the basic biology of adipokines is **derived from human and rodent data**
- **Adipose** tissue is regarded as an **important endocrine organ** that secretes a wide variety of substances including growth factors and cytokines, complement proteins, vasoactive factors, regulators of lipid metabolism, and others
- Collectively, these factors are labeled "adipokines" and they function as part of a complex set of physiologic control systems that regulate local tissue and whole organism physiology
- **Adipokines are defined generally as biologically active substances produced in adipose tissue that act in an autocrine/paracrine or endocrine fashion**
- **Adipokines may contribute to the regulation of biological processes**, including inflammation and immune function, hemostasis, cell proliferation and angiogenesis

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Adipokines (leptin-low is good)

- Leptin is the prototypic adipokine and is the **best characterized** adipokine in domestic animal species
- Leptin is a **167 amino acid protein**
- Both the nucleotide and amino acid sequences are **highly conserved**, with homologies of 83–95% for nucleotide and 79–96% for amino acid sequence in vertebrate species examined
- **Adipocytes are the main site of leptin synthesis** and the main contributor to serum leptin levels
- However, lower levels of expression of leptin mRNA are detectable in other tissues such as placenta, mammary gland, gastric mucosa, and liver
- The **primary actions for leptin are suppression of appetite and increased energy expenditure** (thermogenesis)
- **Fat mass** appears to be the **primary determinant** of serum leptin concentration in the horse
- **Not all overweight horses are hyperleptinemic** (management and feeding practices can affect changes in levels)
- **Not specific for ID or IR in horses**
- Most associated with adiposity (equine)
- Can you manage leptin?

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Adipokines (adiponectin: low levels are BAD; high levels are good)

- Adiponectin has very restricted tissue expression and is thought to be produced almost exclusively by mature adipocytes
- Adiponectin is a **244-amino acid protein**
- In the circulation, **adiponectin** may form **trimers, hexamers, or high molecular weight multimers**
- Currently, it is thought that the **HMW forms have the most biological activity** and are best correlated with insulin sensitivity
- Secretion of adiponectin by fat cells is stimulated by insulin, a number of drugs and dietary constituents modulate blood levels of adiponectin
- Pharmaceutical regulators (humans) of adiponectin expression and secretion are the thiazolidinediones
- In **rodent models**, supplementation with fish oil, linoleic acid, and soy protein increased circulating adiponectin
- Trained athletes usually show an increase in circulating adiponectin while unfit or obese individuals may show a decline in adiponectin levels following exercise
- **(1) Function**: Anti-inflammatory properties (suppress TNF-alpha production by macrophages)
- Suppresses adhesion molecules by endothelial cells

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Adipokines (adiponectin: low levels are BAD; high levels are good)

- Unlike leptin, increases in fat mass result in decreased circulating adiponectin while weight loss results in increased adiponectin (humans), not consistent in horses
- In humans, circulating adiponectin levels are negatively correlated with body mass index, fasting insulin concentrations, and plasma triglyceride concentration but are positively correlated with high density lipoprotein cholesterol concentrations
- Overweight and obese individuals (humans) have a relatively lower proportion of the HMW form of adiponectin compared with other forms, and the **percentage of HMW adiponectin relative to total adiponectin increases with weight loss**
- **Increased production of pro-inflammatory cytokines** such as TNF-alpha and IL-6 as well as reactive oxygen species within the enlarging fat mass
- Hypoadiponectinemia may be an independent risk factor for the development of metabolic and cardiovascular complications
- **(2) Function**: increases insulin sensitivity resulting in decrease insulin levels (equine)
- Circulating adiponectin in horses has been shown to be negatively correlated with fat mass, percent body fat, BCS, and leptin levels (some inconsistent data, but yes, in general)
- Unlike leptin, adiponectin levels do not appear to fluctuate in a circadian pattern, or in response to feeding or exercise
- Based on lab – serum or plasma (**Univ of Penn – SERUM**)

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Adipokines (adiponectin: low levels are BAD; high levels are good)

- **Adiponectin** is a marker of insulin dysregulation/EMS and laminitis risk
- Key regulator of glucose and lipid metabolism and has insulin sensitizing, anti-inflammatory and antioxidant effects
- **Unlike leptin**, low adiponectin is strongly associated with insulin dysregulation and laminitis risk (not just obesity)
- **Low adiponectin is an independent risk factor** and relatively strong predictor of laminitis
- Adiponectin concentrations are:
  - unaffected by stress / feed / grain access prior to sampling
- If possible, it is ideal to **measure both insulin and adiponectin** when screening horses and ponies
- Adiponectin is **most valuable** as a tool to identify horses and ponies with ID and a high risk of laminitis — particularly when they have normal resting insulin
  - Ex. If, evaluating only resting insulin, evaluate both resting insulin and adiponectin, THEN if any horses have low adiponectin, perform OST on those horses
  - If insulin (prefer OST and post-prandial insulin response) and adiponectin are both normal – then likely metabolically healthy

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Adiponectin (Equine)
Van Eps Laminitis and Endocrinology Laboratory

Adiponectin* level (ug/mL)	Interpretation
>10	Healthy
8-10	Equivocal
6-8	Mild risk laminitis (may be normal for Arabian, Quarter horse, WB)
4-6	Moderate risk laminitis
<4	Severe risk laminitis

*Total adiponectin levels

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Adipokines (adiponectin: low levels are BAD; high levels are good)

Normal insulin and low adiponectin

- May be a warning that the horse is more likely to become hyperinsulinemic at other times (especially in response to feed / pasture high in non-structural carbohydrate)
- Although adiponectin is very stable (not affected by feed / stress) insulin is very dynamic
- A low adiponectin level may also make a horse or pony more susceptible to laminitis as a result of high insulin
  - (low adiponectin is an independent risk factor for laminitis — independent of ID status)
  - Similar to humans with metabolic syndrome, adiponectin may be protective against the deleterious effects of EMS / ID
- If further insulin testing is indicated:
  - OST or post-prandial insulin
  - This may identify if insulin levels are an issue under the current management conditions — and how concerned to be if there is pasture acess
  - If further insulin testing is normal, then there is no need to act further
  - Regular monitoring (at least yearly) is indicated
  - If OST / post-feed insulin is elevated, then manage accordingly
    - feed / management changes/pharmaceuticals

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Adipokines (adiponectin: low levels are BAD; high levels are good)

Elevated insulin and normal (high) adiponectin

- A mild increase in insulin (<50 uIU/ml) with normal adiponectin:
  - Maybe, OST or post-prandial insulin (manage as ID)
- In severely hyperinsulinemic animals (>100 uIU/ml), regardless of adiponectin result:
  - Management / feed change and medication, immediately
- **Severe hyperinsulinemia with normal adiponectin is an extremely rare combination**
- Management including diet, weight loss, exercise, and medication **can improve adiponectin concentration over time**
- **Increases in adiponectin can take several months**
- Repeat measurement every 6–12 months as part of a screening program is recommended
- **Serial monitoring** over weeks / months in newly identified ID / laminitis cases **may not be beneficial**
- Breed specific cut-offs? At least maybe in certain breeds
  - Assay cost: verbal around $40.00/sample

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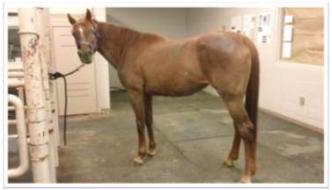
Questions



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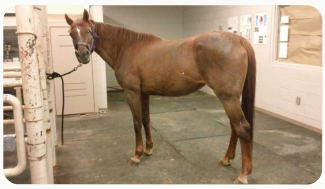
Questions



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Management of the endocrine horse:

The horse owner, the farrier, the veterinarian and the nutritionist

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