Insulin Resistance in Horses

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1. Introduction
Insulin resistance (IR) is important to the equine practitioner because of its association with laminitis. Older horses with pituitary pars intermedia dysfunction (PPID) are pre-disposed to both IR and laminitis, and it is likely that these conditions are related. Horses or ponies that exhibit delayed shedding of the haircoat or hirsutism, loss of skeletal muscle mass, or polyuria/polydipsia should, therefore, be tested for PPID and IR and managed accordingly. There is also a second condition associated with IR in horses, and this syndrome is more challenging to define. Affected horses are described by owners as “easy keepers,” because body weight is maintained on a relatively low caloric intake compared with other horses. In our experience, this condition is most common in ponies, Morgans, Paso Finos, and Norwegian Fjords, but it also occurs in Arabians, Quarter Horses, American Saddlebreds, and Tennessee Walking Horses. Horses with this condition can often be recognized by their appearance. Some exhibit generalized obesity; others are thinner throughout the mid region of the body but suffer from regional adiposity in the form of a cresty neck or enlarged fat pads next to the tailhead. These horses were previously assumed to suffer from hypothyroidism because of perceived similarities between this condition and canine hypothyroidism and the detection of low or low-normal resting serum total triiodothyronine (tT3) and total thyroxine (tT4) concentrations. However, it is now accepted that lower circulating tT3 and tT4 concentrations are a consequence rather than a cause of the horse’s metabolic state, and these concentrations can be attributed to secondary hypothyroidism (decreased thyroid-stimulating hormone release from the pituitary gland) or interference from drugs such as phenylbutazone. Therefore, alternative terms have been adopted to describe this condition in horses and ponies, including peripheral Cushing’s disease, equine metabolic syndrome (EMS), and pre-laminitic metabolic syndrome (PLMS). For the purpose of this discussion, we will use the term EMS to signify this condition, but we will require that all three of the following criteria be met before the term is applied: (1) insulin resistance, (2) history of laminitis or pre-disposition to disease (presence of abnormal growth rings on the hooves), and (3) regional adiposity in the form of a cresty neck or enlarged fat pads.

2. What Is IR?
Physiology Review
Insulin is a hormone secreted by the pancreas that stimulates the uptake of glucose by tissues when sugar is abundant (i.e., after feeding). Skeletal muscle and adipose tissues are the major sites of insulin-mediated glucose uptake, but the liver also
responds to insulin by increasing the uptake of glucose from the blood. Insulin binds to receptors on the surface of plasma membranes. It triggers a series of internal events that results in the movement of glucose-transporter proteins (GLUT4) to the cell surface, which facilitates rapid glucose uptake. Insulin plays an important role in the storage of energy by moving glucose into cells where it can be stored as glycogen or converted into fat.

**IR**

This condition is defined as the failure of tissues to respond appropriately to insulin. There are numerous mechanisms responsible for IR including reduction in the density of insulin receptors on the cell surface, malfunction of insulin receptors, defects in internal signaling pathways, and interference with the translocation or function of GLUT4 proteins.

### 3. IR and Laminitis

All of the pieces of the puzzle must be assembled before we can fully understand the association between IR and pasture-associated laminitis in horses and ponies. There are two broad mechanisms by which IR could pre-dispose horses to laminitis: (1) insulin resistance might impair glucose delivery to hoof keratinocytes, or (2) insulin resistance could alter blood flow to the foot. The first theory is supported by results of a study performed by Pass et al. in which it was shown that hoof tissue explants kept in culture separate at the dermal-epidermal junction when deprived of glucose. Furthermore, Mobasheri et al. determined that GLUT4 proteins are found in equine keratinocytes, which suggests that insulin-stimulated glucose uptake occurs in the hoof. Studies examining the relationship between IR and blood flow have not been performed to date in horses; however, insulin is known to act as a slow vasodilator in humans, and IR has been associated with a decrease in peripheral vasodilation.

If IR is a determinant of susceptibility to pasture-associated laminitis, then what triggers the laminitis episode itself? It seems that non-structural carbohydrates (NSC) within pasture grasses play an important role in this process. Most NSC measurements include simple sugars, starch, and fructans (polymers of fructose), and levels of these components vary considerably within grass according to geographical location, soil type, weather conditions, and time of day. NSC are likely to affect the susceptible horse in two ways. First, excessive sugar consumption could exacerbate IR like it does in diabetic humans. Second, consumption of large quantities of NSC might alter the bacterial flora found within the large intestine. These alterations in bacterial flora are thought to increase the production of as yet unidentified triggering factors for laminitis that may include exotoxins, endotoxins, or vasoactive amines. Alterations in large intestinal bacterial flora have been induced by orally administering oligofructose (a fructan) to horses.

### 4. How Do You Test for IR in Horses?

Ideally, a test that provides a specific measure of insulin sensitivity would be used to assess affected horses, and the frequently sampled IV glucose-tolerance test (FSIGT) or euglycemic hyperinsulinemic clamp (EHC) procedure are available for this purpose. Unfortunately, these tests are technically challenging and require a large number of samples. Practitioners are advised to use two simple but indirect methods of assessing insulin sensitivity:

**Combined Glucose–Insulin Test**

The procedure for the combined glucose–insulin test (CGIT) involves collection of a baseline blood sample, infusion of 150 mg/kg body weight (bwt) 50% dextrose solution, and infusion of 0.10 units/kg bwt regular insulin immediately after the first infusion. Blood samples are collected at 1, 5, 25, 35, 45, 60, 75, 90, 105, 120, 135, and 150 min post-infusion. When this test is used, IR is defined as maintenance of blood glucose concentrations (measured with a hand-held glucometer) above the resting (baseline) value for ≥45 min. The test can be abbreviated to 60 min when used in the field, but it is advisable to complete the measurements so that the time taken for the blood concentration to return to baseline can be recorded for future reference. This allows assessment of the response to diet, exercise, or medication. There is a small risk of hypoglycemia when performing this test. Therefore, two 60-ml syringes containing 50% dextrose should be kept on hand and administered if muscle fasciculations or profound weakness are observed or if the blood glucose concentration drops to <40 mg/dl. Note that stress is an important cause of transient IR that can significantly impact CGIT results. In one of our studies, we detected IR in healthy, non-obese horses when CGITs were performed immediately after endoscopic examinations. Therefore, horses must be kept calm before and during the procedure to avoid false positive results. An IV catheter should be used to reduce the stress associated with blood collections, and ideally, this catheter is placed the night before the CGIT. Because pain affects results, horses suffering from acute laminitis must be given time to recover before testing. Feed deprivation also causes stress, so horses should be permitted to eat grass hay during the testing procedure.

**Measurement of Resting Serum-Insulin Concentration**

This is the easiest measurement to perform, and it is a useful screening test, because compensatory hyperinsulinemia is a common feature of IR in horses. There are, however, two situations where this test will not be helpful. In the first situation, the horse has mild or early IR, and hyperinsulinemia has not developed yet or the rise in serum insulin concentration is too small to exceed the reference range. This problem is magnified by the wide reference ranges currently available for horses and differences...
between laboratories. For instance, hyperinsulinemia is defined as a serum insulin concentration above 30 μunits/ml at the University of Tennessee, whereas the Diagnostic Center for Population and Animal Health at Michigan State University uses a 300 pmol/l (43 μunits/ml; conversion factor approximately equal to 7.0) cut-off value. In the second situation, a horse with pancreatic insufficiency as a consequence of prolonged disease would escape detection if serum insulin concentrations had returned to within the reference range.

Practitioners are advised to screen horses for IR by measuring resting serum-insulin concentrations. The CGIT should also be used to further investigate the normoinsulinemic horse that has a physical appearance consistent with EMS or PPID. Horses should be fasted or fed only grass hay overnight, and stress should be avoided when collecting blood samples. If hyperinsulinemia is detected, this finding is usually sufficient to arrive at the diagnosis of IR; however, horses with serum insulin concentrations that fall within the reference range should be assessed with the CGIT. When measuring insulin concentrations, samples should be sent to a laboratory that is accustomed to handling equine blood and has established reference ranges for horses. Establishment of a reference range for a particular farm is also recommended when serial measurements are to be performed.

5. Management of IR in Horses

The two principal strategies for addressing IR in horses are diet and exercise, but affected horses can be divided into three groups: (1) obese horses with IR, (2) non-obese horses with regional adiposity (cresty neck) and IR (many horses with PPID fall into this category), and (3) severely affected horses from either group that are currently suffering from laminitis.

1. Obese horses with IR should be placed on a diet containing fewer calories and an exercise program to lower body weight and increase fitness. Feeds that contain readily available sugar, such as sweet feed, should be completely eliminated from the diet. If the horse does not suffer from laminitis, it can be allowed to graze on pasture. Clients should be warned that horses with EMS can often maintain their body weight even when grazing is limited, and pasture-associated laminitis remains a risk if the horse is left out on pasture. Strategies to limit the amount of grass consumed include limiting grazing time (1–2 h/day), enclosing the horse in a smaller area using a round pen or electric fence, or using a grazing muzzle.

Hay should be the principal component of the diet along with protein and trace mineral supplements as needed. Analysis of hay is strongly recommended to ensure that the NSC content of the hay is low. Samples can be sent to the Dairy One Forage Laboratory, and the cost of analysis is $25/sample. Hay with a NSC level <12% should ideally be selected for affected horses. If only hay containing a higher level of NSC is available, soaking the hay for 30 min in cold water will reduce the sugar content. Be aware that this process can also leach out other nutrients from the hay. Horses should be exercised as consistently as possible (every day is ideal), and clients should be encouraged to exercise the horse on a lunge line or in hand even if it is lame (excluding those with acute laminitis).

2. Non-obese horses with IR should be placed on a similar diet and exercise program to improve insulin sensitivity but with more calories provided, particularly when the horse is being strenuously exercised. Many horses with PPID fit this description. High glycemic feeds such as sweet feed should be removed from the diet and replaced with fat and fiber. Up to 20% of calories can be provided by fat in the form of vegetable oil or rice bran. Low-starch or low-NSC commercial feeds are also available.

3. Severely affected horses with laminitis should be taken off pasture altogether. Grass hay with a low NSC content should be fed along with concentrates that primarily contain fat and fiber until laminitis has subsided. After the acute phase has passed, obese horses should be placed on a weight-reduction diet composed primarily of grass hay with a low NSC content. Hay should be weighed out to avoid overfeeding. Weight loss can be accelerated in these horses by limiting their caloric intake and administering levothyroxine at a dosage of 4 teaspoons (48 mg) once daily orally for an average-sized horse. Levothyroxine reduces body-fat mass and improves insulin sensitivity in horses that are kept off pasture and maintained on a controlled diet. Treated horses should be weaned off the drug after the ideal body weight has been attained by reducing the dosage to 2 teaspoons (24 mg) once daily orally for 2 wk and then 1 teaspoon (12 mg) once daily orally for 2 wk. Some horses that suffer from chronic laminitis in association with EMS must be kept off pasture indefinitely.

References and Footnote


"Thyro L, Lloyd Inc., 604 West Thomas, Shenandoah, IA 51501."