Insulin dysregulation in equine metabolic syndrome and pituitary pars intermedia dysfunction

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Insulin dysregulation is an endocrine abnormality defined as basal hyperinsulinemia, insulin resistance and/or postprandial hyperinsulinemia. Insulin dysregulation (ID), specifically postprandial hyperinsulinemia, is the critical component that leads to laminitis in horses with equine metabolic syndrome (EMS) or pituitary pars intermedia dysfunction (PPID).

Equine metabolic syndrome is not a disease, rather a collection of risk factors for hyperinsulinemia-induced laminitis. The consistent abnormality of EMS is ID. Pituitary pars intermedia dysfunction (PPID) is a common endocrine disorder of the older horse and pony. The prevalence of PPID in ponies and horses over 15 years of age is over 20%, but PPID rarely occurs in equids less than 10 years old. The endocrine disorder can be associated with ID leading to laminitis, but many horses have PPID without ID.

Diagnostic tests for ID

The primary recommended diagnostic test for insulin dysregulation is standardized administration of oral glucose and measurement of the insulinemic response. The most common diagnostic test is the oral sugar test (OST). In Sweden, a protocol with administration of Dansukker glucose syrup (0.2 mL/kg) has been established. In the field, the postprandial response can be determined using a single sample obtained between 1 – 1.5 hours after glucose administration. The insulin concentration obtained between 1 – 1.5 hours is used to diagnose horses with ID. Insulin concentrations are highly variable between methods for insulin analysis. Therefore, correct reference values are needed for the interpretation of test results for each method. In **table 1**, test results for insulin determined by the Mercodia Equine Insulin ELISA using an oral sugar test are displayed.

Table 1: Interpretation of test results for the oral sugar test using the Mercodia Equine Insulin ELISA.

Insulin concentration at 1 – 1,5 hours	Interpretation
< 45 mU/L	Normal insulin regulation
45 – 100 mU/L	Mild insulin dysregulation
> 100 mU/L	Moderate insulin dysregulation
> 200 mU/L	Severe insulin dysregulation

Lifestyle interventions in horses with ID

Horses with ID respond to intake of non-structural carbohydrates (NSC) with excessive postprandial hyperinsulinemia. Therefore, decreasing excessive hyperinsulinemia is crucial in preventing laminitis in these horses. The current strategy is to keep the intake of NSC low and, when appropriate, improve tissue sensitivity by promoting weight loss and increasing exercise. Concentrated feed should be avoided. Insulin dysregulated horses should be fed hay or haylage with a water-soluble content (WSC) of < 100 – 120 g/kg feed on a dry matter basis (< 10 – 12%). To decrease the WSC content further the hay or haylage can be soaked in water before feeding. The feeding can be divided into more rations

per day in order to attenuate the insulin response, thereby decreasing the risk for excessive postprandial hyperinsulinemia. ***When appropriate changes have been made in feeding and management it is advised to evaluate if the postprandial insulin response is low enough in order to decrease the risk for laminitis.*** A dynamic meal tolerance test (D-MTT) evaluates the postprandial insulin response on the horse's regular feed (hay or haylage). The largest meal of the day should be fed in the morning (hay or haylage). A single blood sample should be taken 2 – 2.5 hours after the meal of hay or haylage has been given. The blood sample should be analyzed for insulin using the Mercodia Equine Insulin ELISA. Postprandial insulin samples > 150 mU/L suggest increased risk for laminitis whereas postprandial insulin samples < 100 mU/L indicate low risk for laminitis.

Complementary pharmacological treatment of insulin dysregulation

In some horses with marked ID, intake of hay or haylage with very low NSC still results in excessive postprandial hyperinsulinemia. In these horses, pharmacological treatments that efficiently decrease postprandial hyperinsulinemia are needed. ***These treatments should never replace lifestyle changes***. Metformin hydrochloride is the most commonly suggested pharmacological treatment for horses with excessive ID, but it has recently been shown that the drug has no effect on the postprandial insulin response in naturally occurring ID.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new treatment option for human adults with type 2 diabetes mellitus (T2DM). These drugs decrease hyperglycemia in T2DM patients by inhibition of glucose reabsorption in the proximal tubules in the kidneys, resulting in glucosuria. The increase in urinary glucose excretion is partly balanced by increasing hepatic glucose production, resulting in improved glycemic control with low risk of hypoglycemia. We have recently demonstrated that 3 weeks of treatment with SGLT2 inhibitors decreases the postprandial insulin response on average by 66% in ID horses. The horses did not demonstrate hypoglycemia or urinary tract infections. The horses lost weight during the treatment when the feeding was kept constant, but the magnitude of the weight loss varied highly between horses. The risk for urinary tract infections appear to be very low in ID horses treated with SGLT2 inhibitors but the risk for increase in liver enzymes and triglycerides is high. A tight balance between feeding and treatment with SGLT2 inhibitors is necessary to avoid side effects. Simplified methods to evaluate horses on treatment are therefore needed. Currently, we have several studies in progress including two PhD-projects using SGLT2 inhibitors in horses. The oral presentation will cover some preliminary data from these studies and discuss some practical problems with safe treatment of horses with SGLT2 inhibitors. In recent years, several SGLT2-inhibitors have been used in horses (**Table 2**).

Table 2: SGLT2-inhibitors in horses

SGLT2-inhibitor	Dose
Canagliflozin	0.4 – 0.6 mg/kg PO q 24 hr
Dapagliflozin	0.02 mg/kg PO q 24 hr
Ertugliflozin	0.05 mg/kg PO q 24 hr

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