Myths and Truths of Equine Metabolic Syndrome

Steven F. Skinner, DVM, SHP

In this lecture we will be looking at some of the various myths and truths about an important equine disorder, equine metabolic syndrome. We must first evaluate several different disorders which have many the same clinical signs. The first disorder is primary adrenal gland dysfunction and the second is a pituitary pars intermedia dysfunction (PPID). The third disorder we will be discussing is diabetes mellitus (DM). The fourth disorder will be equine metabolic syndrome (EMS). These disorders are hard to diagnosis and many times misdiagnosed. They can be difficult to identify because of the closeness of the clinical signs.

Cushing's disease can be a primary adrenal disorder or a secondary disorder caused by a tumor in the pituitary. The primary disorder is caused by the hypertrophy of the cells in the adrenal gland or a tumor in the adrenal gland. The hypertrophy increases the production of cortisol which in turn produces the release of cortisone, which produces the abnormal effects seen. The second abnormality which is seen in some animals are adrenal tumors, but do not occur in the equine.

Pituitary pars intermedia dysfunction (PPID) is a dysfunction caused by a tumor in the pars intermedia of pituitary gland. The age of onset of this disorder in the equine is between 16 and 40 years. The clinical signs seen are the result of an increased release of adrenocorticotropic hormone (ACTH), which in turns increases the release of cortisol from the adrenal gland and increased circulation of cortisone, producing the

clinical signs. The clinical signs seen in both of these disorders are 1) hirsutism - defined as delayed or failed shedding of the winter hair coat, 2) excessive sweating, 3) polyuria/polydipsia, 4) skeletal muscle atrophy, 5) cresty neck, 6) laminitis, 7) insulin resistance(IR) and with a brain tumor possible behavioral abnormalities, blindness, and seizures. The clinical signs that we see in this disorder are related to the increased cortisone production and its effects on varying tissues. The cortisone increase also plays a role in the insulin production as the high levels of cortisone may inhibit the uptake of glucose into cells. Insulin resistance may occur because of this. It is my belief that this disorder is over-diagnosed in veterinary medicine. There are two diagnostic tests used to diagnose this disorder. The first is a dexamethasone suppression test. Dexamethasone is a corticosteroid and it is injected intravenously to the equine. Measurement of blood cortisol is performed before the injection of dexamethasone and in 24 hours following the injection. In the normal patient the cortisol level will be decreased in 24 hours. If Cushing's disease is present then the cortisol level may be increased in 24 hours. The second test used is the ACTH stimulation test. ACTH is injected intravenously and a baseline cortisol level and a 4 to 8 hour post-injection cortisol level is performed on the blood. In the disease state the cortisol level in the blood will be approximately four times that of the baseline level. Other tests used to identify pituitary tumors are the CT scan or MRI. In the equine these tests are much more difficult to perform. In other animals the treatment for primary adrenal dysfunction is surgical removal of the involved adrenal gland. This is impractical in the equine at this time. The treatment for PPID in the equine is pergolide, a dopamine agonist. This drug is relatively expensive and the dosage is .5 to 2 mg per day. The lower dose range would be started and in 4 to 6 weeks a dexamethasone suppression test is performed. If there is suppression

of the cortisol the pergolide dosage would not be changed and would be continued for life. If there is no suppression the dosage would be increased and the dexamethasone suppression test performed again in 4 to 6 weeks until there is suppression. This dose will be continued for life. The other drug which has been used is cyproheptadine, an antihistamine. The dose is .25 mg/kg/day. There is not good evidence that this drug helps in this disorder. Supportive care given horses with Cushing's disease includes general good hygiene, exercise to keep up muscle tone, and the feeding of a good complete diet to prevent obesity. Success treating these patients is not extremely successful.

The third disorder we are discussing is diabetes mellitus. This disorder is caused by a loss of the beta cells in the pancreas. Histological examination of the pancreas in these patients indicate that there is a partial or complete loss of the beta cells. Without beta cells the pancreas cannot produce insulin. Insulin regulates glucose uptake into cells. Without insulin the glucose builds up in the blood producing hyperglycemia. The clinical signs seen in this disorder include excessive thirst, increased urine output, glycosuria, a thick cresty neck, and laminitis. It is been found in recent years that this disorder is occurring more frequently in the equine than previously thought. The diagnosis of this disorder is accomplished by repeated glucose levels in the blood, looking for the level to be greater than 122 - 150 mg/dL. The other test which is frequently used as a glucose tolerance test which measures the ability of the glucose level to return to the baseline level over a period of time. The insulin level in the blood can be measured and is found to be extremely low. The treatment of diabetes is accomplished by using various compounds of insulin given by injection. Horses with diabetes must be fed very carefully with a high quality food, attempting to maintain stabilization in the blood glucose. Measurement of the

glucose level in the blood must be done frequently to make sure that the correct dosage of insulin is being given.

Equine metabolic syndrome is a disorder which has become very important during the past 15 years. It was first described by Dr. Johnson in 2002, when he described a disorder that included obesity, insulin resistance (IR), and laminitis. Dr. Nicholas Frank studied this disorder during the next 10 years and in 2010 he and a group of equine practitioners developed the ACVIM's consensus statement, with the phenotype including: 1) increased obesity, 2) insulin resistance(IR), 3) laminitis as the primary elements. Additional components include hypertriglyceridemia, hyperleptinemia, and atrial hypertension, altered reproductive cycling in mares, and increased systemic markers of inflammation in association with obesity. Today I feel we must consider this disorder, primary when we see the above indications. The clinical signs observed in this disorder are regional obesity, overall obesity, bilateral lameness due to laminitis or a history of a previous laminitis or founder, a cresty neck score of greater than 3 on a scale of 1 to 5. Meaning that more fat is deposited in the middle of the neck then at the poll or the withers. The adiposity makes these horses lethargic and not wanting to move. The metabolic abnormalities seen in EMS causes the horse to put on weight. Changes in a horse's environmental status may allow for the development of obesity. Adipose tissue is no longer regarded as just an energy storage organ but also as an endocrine organ producing hormones which may contribute to the development of IR. One of these hormones, Leptin, helps with the feeling of being satisfied after eating. This hormone also may become resistant and the horses may not get satisfied and will continue to eat contributing to the obesity. The abnormalities of the hormones in the fat produce a chronic low-grade inflammation throughout the body. Insulin resistance occurs because there is metabolically an inability of cells to take in glucose for

energy. Increased insulin is released from the pancreas because of this increasing the circulating insulin level. The excess glucose is converted to fat and deposited in the adipose tissue and other body organs such as muscle, liver and pancreatic tissue. Histologically there are no cellular changes in the pancreas that can contribute to the increased insulin in the blood. The development of laminitis is thought to be a result of the hyperinsulinemia which contributes to vascular changes in the laminar corium due to the vasoregulatory effects of insulin. Vasoconstriction is present decreasing the blood supply to the laminar corium producing the inflammation and laminitis seen with his disorder. Other metabolic abnormalities which are produced in EMS most likely contribute to the laminitis also. The diagnosis of EMS includes a history and physical examination, evaluating the horse for regional adiposity, a cresty neck and body condition scoring, and evaluating the hooves for evidence of laminitis either acute or chronic. Laboratory testing includes glucose levels which are usually near the high end of the reference range. Evaluation of blood for insulin is done and usually this value is greater than 20 uU/ml. This test must be done after a period of fasting and the horse not under any sort of stress. As food and stress will alter the insulin levels. The other dynamic test done is a combined glucose-insulin test (CGIT). Blood samples are obtained to measure the baseline glucose and insulin levels. 150 mL of a 500 mg/mL glucose solution is administered IV, followed IV by a .5 mL of a 100 unit per milliliter regular insulin solution. Glucose levels are drawn at time zero, 30, 45 and 60 minutes. Insulin levels are drawn at 0 and 45 minutes time. Blood glucose levels should be below the baseline levels in 45 minutes. Insulin levels of greater than 100 micro units per milliliter at 45 minutes is an indication that the secretion of insulin greater than normal or the clearing of insulin from the circulation is at a slower rate than normal, both of which indicate EMS. In the future

other testing may include metabolic analogues such as adipokines, lipids, fructosamine or C-reactive protein. Some recent studies looking at inflammation and metabolic analogues have indicated that these are elevated in EMS. As can be seen EMS is a multifactorial disorder. Comprising many metabolic changes in the horse. This disease is also seen in humans and has been studied intensively. There are no specific treatments for this disorder but the following are extremely important

1) Dietary management - reduce weight by reducing the amount of energy provided in the diet, eliminate pasture grass from the diet totally, use a lower energy grass hay fed at 1.5 pounds per 100 pounds body weight, with a supplement of a commercial high-quality protein diet and a mixture of vitamins and minerals.

2) Physical activity - 2 to 3, 20 to 30 minute sessions per week, starting gradually and increasing to more vigorous sessions 5 times a week

3) It has been shown that EMS, the insulin resistance and laminitis associated with it return to normal once obesity is controlled.

4) It may be a benefit to give thyroxine (a hypo-thyroid medication) as a way to induce weight loss. It is also been seen that insulin sensitivity has improved. The dosage is approximately 48 mg per day in a horse 350 kg or greater. As the ideal body weight is achieved this dosage is reduced. Metformin a biguanide drug enhances the action of insulin within tissues. This drug has not been evaluated for side effects, but so far all indicators are positive.

It has been found that the clinical signs of EMS and the insulin levels return to normal when weight loss is achieved. There is still a lot to be learned about the metabolic ramifications of this disorder. Future studies will most likely add light to this complicated and frustrating disorder.