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SYMPOSIUM

Diabetes, Insulin Resistance, and Metabolic Syndrome in Horses

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Abstract

Analogous to the situation in human medicine, contemporary practices in horse management, which incorporate lengthy periods of physical inactivity coupled with provision of nutritional rations characterized by inappropriately high sugar and starch, have led to obesity being more commonly recognized by practitioners of equine veterinary practice. In many of these cases, obesity is associated with insulin resistance (IR) and glucose intolerance. An equine metabolic syndrome (MS) has been described that is similar to the human MS in that both IR and aspects of obesity represent cornerstones of its definition.

Unlike its human counterpart, identification of the equine metabolic syndrome (EMS) portends greater risk for development of laminitis, a chronic, crippling affliction of the equine hoof. When severe, laminitis sometimes necessitates euthanasia. Unlike the human condition, the risk of developing type 2 diabetes mellitus and many other chronic conditions, for which the risk is recognized as increased in the face of MS, is less likely in horses. The equine veterinary literature has been replete with reports of scientific investigations regarding the epidemiology, pathophysiology, and treatment of EMS.

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Insulin Resistance in Horses: An Equine Metabolic Syndrome

Increasing recognition of the relevance of insulin resistance (IR) to health in horses has somewhat paralleled that reported in the human medical field.[1–3] Although specific definitions differ somewhat, the presence of IR is an important component of metabolic syndrome (MS) in human patients.[4–6] Other clinical abnormalities that contribute to the definitions of MS include an increased body mass index, central obesity, hypertriglyceridemia and dyslipidemia, elevated blood pressure, microalbuminuria, and elevated biomarkers for the

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Abbreviations: (CGIT) combined intravenous glucose–insulin test, (DM) diabetes mellitus, (EMS) equine metabolic syndrome, (HbA1c) glycosylated hemoglobin, (IR) insulin resistance, (MS) metabolic syndrome, (NSC) nonstructural carbohydrate, (PPID) pituitary pars intermedia dysfunction

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presence of inflammation.[4–6] The presence of MS in human patients portends greater risk for development of many important chronic disease conditions, including diabetes mellitus (DM), cardiovascular disease, stroke, Alzheimer's disease, prostatic disease, overactive bladder syndrome, gout, polycystic ovary disease, asthma, sleep apnea, psoriasis, gall stones, fatty liver disease, nonalcoholic steatohepatosis, and all-cause mortality.[7–18]

The American College of Veterinary Internal Medicine commissioned a panel of specialists interested in equine metabolic syndrome (EMS) to develop a consensus statement that has provided a syndrome definition based on current knowledge.[2] Demonstration of IR in horses with aspects of obesity represents the cornerstone of the EMS definition, as it does in the human syndrome. Similar to human MS, there is now evidence that EMS-affected horses can be further characterized by demonstrating upregulated markers of inflammation[19,20] and a propensity to develop arterial hypertension.[21,22] Other clinical and laboratory abnormalities that may eventually be helpful for definition of EMS include infertility, hypertriglyceridemia, and hyperleptinemia.[2,23]

Clinical recognition of EMS portends increased risk for the development of several important equine diseases, including laminitis ("founder"), hyperlipemia syndrome (hepatic lipidosis), osteochondrosis, and type 2 DM.[1–3] Laminitis is a common, painful equine condition in which lameness results from abnormalities of growth and degenerative changes in the hoof lamellar interface, the epidermo–dermal connection that attaches the hoof wall to the underlying connective tissue of the third phalanx (responsible for weight bearing in this species). Laminitis represents the most common clinically important chronic disease for which identification of EMS contributes increased risk.[1–3]

The equine hyperlipemia syndrome (hepatic lipidosis) is similar to nonalcoholic steatohepatosis and is most commonly identified in those relatively "thrifty" (metabolically efficient) equine breeds in which pronounced IR appears to result from inherited factors (especially certain pony breeds and miniature horses).[24,25] The development of osteochondrosis, a common developmental orthopedic disorder that affects young, growing horses that have been fed rations characterized by excessively high dietary energy content has been linked to the presence of IR.[26] As with their human counterparts, horses may develop type 2 DM as a result of IR and EMS, but DM is relatively uncommonly identified in the equine species.

Diabetes Mellitus in Horses

Development of overt DM, as characterized by marked hyperglycemia resulting from lack of insulin or insulin effect (IR) has been rarely reported in horses.[27,28] Hypertriglyceridemia may also occur as a result of DM (insulin normally acts to stimulate lipoprotein lipase and offset the development of hypertriglyceridemia).[29] Although diabetes in human medicine may be classified as insulin-dependent DM (or type 1) or noninsulin-dependent DM (or type 2), these distinctions have not been applied extensively in the equine veterinary field.[30,31] Secondary DM (type S), impaired glucose tolerance, and gestational diabetes are other categories of classification that are described in the human literature.[31]

The equine veterinary literature concerning DM includes several references to the development of IR, attributable to hyperadrenocorticism resulting from pituitary pars intermedia dysfunction (PPID).[27,32] These cases are best classified as examples of type 2 DM when compared with the human field.[30]

As an herbivorous species, the equine pituitary gland has a well-developed "intermediate lobe" that secretes several proopiomelanocortin peptides or "melanocortins" (corticotropin, beta-endorphin, alpha-melanocyte-stimulating hormone, and corticotropin-like intermediate peptide) that are important for the seasonal physiological adaptations in readiness for winter.[32] Throughout most of the year, the secretion of pituitary-derived melanocortins is inhibited by dopaminergic nerves that originate in the hypothalamus. Melanocortin secretion is normally enhanced in the autumn when it serves to stimulate lipogenesis, thickening of the hair coat, and weight gain in readiness for winter. One of the most common endocrinopathic conditions of mature horses, PPID results from an age-associated, oxidative stress-mediated degeneration of the dopaminergic nerves critical for intermediate lobe inhibition.[33] Therefore, in some respects, PPID of horses bears similarity to Parkinson's disease in people.[34] Insulin resistance is commonly identified as a component of the clinical abnormalities that result from PPID in these older horses.[32,35]

It has been suggested that type 2 DM occurs to a greater extent than previously believed in horses affected with PPID.[27] The presence of marked IR and severe pancreatic β-cell dysfunction was confirmed in three PPID-affected horses using an insulin-modified frequently sampled intravenous glucose tolerance test coupled with a minimal model analysis of insulin–glucose dynamics.

Normoglycemia was reestablished in each of these horses following treatment with a combination of dietary modification, metformin, glyburide (also referred to as glibenclamide), and pergolide (dopaminergic agonist).[27]

A few cases of *bona fide* DM have been reported to develop in adult horses.[28,30,36–44] Specific causes for DM that have been described in horses have included chronic pancreatitis,[36–38] ovarian neoplasia,[39] pregnancy,[30] and immune-mediated polyendocrinopathy.[40] Transient DM was also identified in a 3-day-old foal that presented with diarrhea.[45] In that case, type 1 DM was considered likely (hyperglycemia in the absence of hyperinsulinemia and a positive response to administered insulin), similar to neonatal DM in human babies.[46] Treatment of DM in that foal using protamine zinc insulin for 26 days resulted in a successful outcome and the foal was normal at 11 months of age.[45] The authors speculated that both the diarrhea and DM may have resulted from coronavirus infection, which has been identified as a cause of pancreatic damage in other species.[47–50]

Extensive endocrinological testing (including determinations of circulating plasma insulin concentration) is infrequently reported for horses in which DM is reported. In one clinical report of DM in an adult horse, immunohistological examination of the pancreas *post-mortem* revealed a marked paucity of β cells at the periphery of the islets of Langerhans.[28] Evidence for islet amyloidosis, as has been described as a component of DM in several other species, has not been reported in horses.

Elevated levels of glycosylated hemoglobin (HbA1c) and fructosamine represent reliable methods for identifying human patients with undiagnosed DM who are at risk for developing diabetic complications.[51,52] Determinations of HbA1c and fructosamine are widely adopted as useful indices of mean blood glucose during treatment of DM in humans because they can be performed at any time of day without special patient preparation. Moreover, HbA1c is less affected by daily or weekly variations in glucose concentrations than fructosamine or single plasma glucose values.[53] This minimizes the overinterpretation of transient hyperglycemia during the management of DM. The clinical utility of HbA1c and fructosamine has not been extensively evaluated in horses because DM is rare in this species. Although the measurement of HbA1c in one diabetic horse failed to demonstrate an elevated result, both HbA1c and fructosamine were elevated in another horse affected with DM.[28,40]

The long-term management of insulin-dependent DM in a horse affected with immune-mediated polyendocrinopathy has been reported.[40] In that case, favorable clinical results, including weight gain, return to exercise, and reduced voluntary water consumption, were achieved by providing a special diet and administering an intermediate-acting insulin, neutral protamine Hagedorn (Humulin® N; Eli Lilly), once daily over the course of 18 months.[40] Treatment resulted in partial glycemic control as assessed by improved measurements of both blood glucose concentration and HbA1c. That particular horse subsequently died as a result of both worsening DM and adrenocortical failure.

Diagnostic Approach for Insulin Resistance and Diabetes in Horses

Assessment of the patient's medical history, results of the physical examination, evaluation of radiographs of the feet (for laminitis), and results of laboratory tests all contribute to the clinical diagnosis of EMS or DM. Although the euglycemic hyperinsulinemic clamp technique and the frequently sampled intravenous glucose tolerance test have been adopted for use in horses as the "gold standard" tests for IR, these methods have been used mostly in research settings.[2] For veterinary clinical practice, alternative but less specific diagnostic approaches are generally used.[1–3]

Fasting concentrations of both insulin [reference range, <20 μU/ml (<144 pmol/liter)] and glucose (reference range, 80–115 mg/dl) tend to be relatively constant and may be used to provide insight into the equine patient's insulin sensitivity.[2] In most IR-affected horses, a state of compensated IR is demonstrated by normoglycemia (or slight hyperglycemia) coupled with hyperinsulinemia. Unfortunately, different veterinary laboratories employ different assay methods, so a universally accepted cutoff for significant hyperinsulinemia has not yet been agreed upon.

Clinical identification of hyperinsulinemia by equine veterinarians has become a very important component of both equine clinical practice and equine research.[1–3] Aside from its value in the diagnosis of EMS and IR, the determination of circulating equine insulin concentration is important for the characterization of PPID, osteochondrosis, hyperlipemia syndrome, and DM. The commonly available laboratory methodologies for insulin determination in equine blood use either human or porcine diagnostic assay techniques (with validation), based on the fact that the molecular structure of insulin

is highly conserved across mammalian species.[54] A study applied identical validation protocols to all of the insulin immunoassays currently available in order to identify which ones were accurate and reliable for measuring equine insulin concentrations in equine plasma samples.[54] In that study, several commonly used assays were shown to perform poorly, but the authors identified a commercially available radioimmunoassay method based on recombinant human insulin that performed satisfactorily.

Of interest is the fact that some EMS horses tend to develop reduced glycemic control (hyperglycemia, >150 mg/dl) and may be characterized with type 2 DM.[27] Although the extent to which type 2 DM develops in mature IR-affected horses is unknown, it may be more common than generally thought.

Testing the resting serum insulin concentration as a test for IR in fasted horses appears to be insensitive in some cases.[2,3,55] Therefore, dynamic endocrine testing is recommended for those potential EMS candidates for which resting serum insulin and glucose concentrations are within reference intervals.[2] Clinically practical dynamic tests for IR in horses include the combined intravenous glucose–insulin test (CGIT) and an orally administered sugar test.[2,3,56,57]

The CGIT is performed on fasted horses by administering both glucose and insulin (glucose, 150 mg/kg; insulin, 0.1 U/kg) and measuring the blood glucose concentration over the course of 2 h, typically using a handheld glucometer that has been validated for use in horses. The CGIT outcome is characterized by a two-phase curve with positive (hyperglycemic) and negative (hypoglycemic) portions.[56] Normal insulin sensitivity is associated with a return to baseline within 45 min. The test result is strengthened by measurement of the patient's serum insulin concentration at the +45 min time: demonstration of IR is further supported by a serum insulin concentration of >100 μU/ml at that time. The CGIT is a practical clinical measurement of insulin sensitivity because it provides integrated information and more information than either a singular glucose tolerance test or an insulin sensitivity test.[2,56]

The orally administered sugar test has been introduced for identification of IR in EMS candidates.[57] This test is performed after the patient has fasted overnight and consists of administering Karo light corn syrup (75 ml for a 500 kg horse) to the patient and drawing a blood sample between 60 and 90 min later. A serum insulin concentration of >60 μU/ml at that time is supportive of the presence of IR. Glucose or dextrose powder (1 g/kg body weight) may be used as an alternative to Karo syrup.[3]

As a prey animal, the equine species is characterized by a highly developed "flight" response. Elevated circulating concentrations of stress hormones resulting from fear, excitement, pain, and disease are well-recognized potential confounding factors during the clinical assessment of insulin sensitivity in horses. The clinical administration of dynamic endocrine testing (such as the CGIT) may therefore yield false positive results for IR if the patient is affected by stress.[56] Similarly, the period of evaluation during which a CGIT is undertaken is quite short and may not be accurately representative of the patient's endocrinologic status.

Continuous glucose monitoring represents a technological innovation that has been developed in the human medical field for purposes of better studying glucose regulation in diabetes patients.[58,59] Briefly, this method entails placement of a tiny glucose sensor in a subcutaneous location and computerized digital recording. Using this method, it is possible to unobtrusively record the concentration of glucose in the interstitial tissue compartment (equivalent to the blood glucose concentration) every 5 min over the course of up to 7 days (288 data points per 24 h period).[58,59] Potential advantages of this method for equine practitioners includes the ability to monitor changes in interstitial tissue glucose concentration over time with minimal need for handling. Using this technique, we have observed that the interstitial glucose concentration of lean, insulin-sensitive adult horses tends to be maintained at the lower end of the reference range with minimal variance [horses being fed *ad libitum* low-nonstructural-carbohydrate (NSC) grass hay]. In contrast, the interstitial glucose concentration of obese horses in which IR has been demonstrated using CGIT tends to be more variable over time, runs relatively high within the reference range, and frequently exceeds the high end of the reference range.[55] We have also demonstrated that, when undertaken at the same time as a standard CGIT, there is very high correlation and concordance between results for both methods.[60]

Management and Pharmacotherapy of Insulin Resistance and Diabetes Mellitus in Horses

Management and treatment options for EMS are determined by a full evaluation of the individual patient's specific

clinical circumstances.[1–3] Ideally, however, veterinary clinical recognition of EMS primarily serves to facilitate prevention of laminitis in EMS-affected horses and ponies. If EMS is diagnosed before painful laminitis has occurred, the following preventive strategies are generally recommended: reversal of obesity (when applicable) through both dietary change and increased physical activity; dietary change aimed at reducing the glycemic index of the ration; increased level of physical activity; avoidance of pasture grazing for susceptible individuals (pastures represent an important source of NSCs), especially at certain times of the year and times of the day; and the initiation of critical evaluations of the patient's hoof (based on appearance and radiographic characteristics), with a view to promoting hoof care practices (farriery) that should reduce the risk of laminitis.[55]

Unfortunately, when EMS is diagnosed after painful laminitis has occurred, the application of increased physical activity is not possible because it leads to the worsening of damage in the hoof-lamellar interface. In these cases, treatment of laminitis must be based on critical evaluations of the patient's hoof (after reviewing the appearance and radiographic characteristics of the hoof). In the absence of increased physical activity, the reversal of obesity (if applicable) is primarily based on dietary change. Dietary adjustments must strive to deliver a ration that is characterized by a low NSC content (low glycemic index) in order to both address obesity and minimize phases of hyperinsulinemia that are exacerbative to the laminitic condition.[55,61]

As is the case in other species, dietary management represents a very important component of treatment of both IR and DM in horses. The optimal diet for management of DM in horses is unknown, but a low glycemic ration characterized by high fiber content, low NSCs, and added calories in the form of fat is regarded as a logical choice.[1–3] Specialized commercial rations that are characterized by a low glycemic index and low NSC content are marketed for horses, especially those affected by obesity and IR.

Although exercise has been shown to improve insulin sensitivity in horses,[62–64] it may result in hypoglycemia in horses affected with type 1 DM as it does in human patients.[40,65] Increased levels of exercise are strongly recommended for horses affected with EMS and IR.[1–3,55]

Dietary supplementation using levothyroxine sodium is commonly recommended to promote weight loss and to increase insulin sensitivity.[2,3] The use of certain insulin-sensitizing drugs as a component of the management of IR is beginning to gain acceptance in some cases.

Although both metformin and glyburide have been advocated to promote insulin action in the management of EMS and DM in horses, the scarcity of the condition has precluded significant discussion regarding the potential role of either drug for this species. Metformin is potentially helpful because it inhibits hepatic gluconeogenesis and fatty acid oxidation, reduces intestinal absorption of glucose, and enhances tissue insulin sensitivity.[66,67] However, the oral bioavailability of metformin in horses appears to be low, and further investigation of a suitable method of administration in horses is needed.[68] Glyburide may be helpful for the management of IR and type 2 DM because it promotes the release of endogenous insulin from β cells.

Pioglitazone hydrochloride, a thiazolidinedione, has efficacy to reduce obesity-associated inflammation in humans. This drug has been shown to improve insulin sensitivity in other species and to be orally bioavailable in horses.[69–71] However, preliminary studies have not demonstrated an insulin-sensitizing action for pioglitazone when administered to horses. Further investigations into the dose requirements for this species are being undertaken.[69–71]

Conclusions

Equine metabolic syndrome is being increasingly identified in domesticated horses, and comparisons to predisposing factors in the human population, specifically physical inactivity and the provision of rations that provide excessive dietary energy coupled with high glycemic indices, have been blamed. As with their human counterparts, horses are prone to develop obesity and IR. Laminitis is a potentially crippling condition of horses' feet that represents the most common complication of EMS. Unlike humans, the complicating development of overt DM is not commonly identified in horses, possibly a consequence of their being an herbivorous species with a relatively shorter lifespan. Veterinarians working with horses must arm themselves with the diagnostic and therapeutic tools needed to characterize EMS and reverse its medical implications. The equine veterinary literature has been replete with reports of scientific investigations regarding the epidemiology, pathophysiology, and treatment of EMS.

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