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a bi-monthly electronic newsletter for the veterinary community

Abaxis
3240 Whipple Road
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VetCom

WELCOME!

Happy Holidays!

Welcome to the December issue of VetCom. In this month's issue of In the Trenches we expand upon the controversial issue of hypothyroidism in horses with a discussion of equine Metabolic Syndrome by Dr. Philip Johnson of the University of Missouri. We will wrap up this series next time with an approach to differential diagnosis of equine hypothyroidism and supplementation.

We have a number of new and special offers to announce this month, including: our new VetScan Externship, the new VetScan Message Boards, a drawing for free NAVC attendance and a free Test Drive program for folks interested in taking a look at the VetScan solution to in-clinic diagnostics with no strings attached (we'll even give you 25 free profiles-

In the Trenches

Metabolic Syndrome in Horses

from ACVIM 2003 *—with permission Philip J. Johnson, BVSc, MS, MRCVS, DACVIM Columbia, MO*

INTRODUCTION

A common and well-recognized, but incompletely understood, medical problem that afflicts mature horses has been variously referred to as "hypothyroidism" and peripheral Cushing's syndrome. In many respects, this medical problem of horses is similar to a human condition that had also been referred to by a wide variety of different names and has recently been designated "Metabolic Syndrome" by the W.H.O. In this article, we will describe the Equine Metabolic Syndrome and discuss some of the similarities with the human condition. Our characterization of this syndrome in horses is a work in progress (as it is in the human condition) and new information continues to facilitate a

have a Wellness Day, lab work is on us!) Be sure to take a peek at the VetScan News and Special Offers Section to get all the details!

Guerilla Marleting's Golden Rule #43 Companies that think of what they can give to people fare better than those that think of what they can take.

Some companies (clinics) are givers that relish giving things away to entice prospects and breed client loyalty; others are takers that offer nothing for which they don't charge....

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better and more detailed understanding of its pathogenesis and implications.

CLINICAL PRESENTATION

Affected horses tend to be aged between 6-to-20 years and there does not appear to be a sex predilection. The problem is reported more commonly in some pony breeds, domesticated Spanish mustangs, Peruvian Pasos, Paso Finos, European Warmbloods, American Saddlebreds, and Morgan horses. Affected horses are commonly obese and develop excessive adiposity at specific locations, especially in the crest of the neck, at the shoulders, above the gluteal muscles, and in the sheath (geldings). Female horses are notoriously difficult to breed and exhibit abnormal ovarian cycling behavior. Horse owners refer to many of these horses as "easy keepers" and vigorously contend that all efforts to reduce the horse's obesity by dietary restriction are futile. Ample intra-abdominal (omental) adiposity is evident during ultrasonographic examination of the abdomen or at

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from Guerilla Marketing Excellence, JC Levinson

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For those of you considering a new in-clinic lab, check out our Test Drive program, the 25 free profiles is a great opportunity to provide a "discount" lab day to show your clinic as a dedicated "giver".

necropsy of affected horses. Many of these horses are presented to veterinarians for diagnosis of lameness attributable to laminitis. There is a very strong association between the development of obesity, metabolic syndrome and the risk for developing laminitis. Commonly, at initial veterinary examination, there already exists both physical and radiographic evidence for long-standing laminitis in these horses although reputable and credible owners and managers report that there have been no prior signs of laminitis or any obvious explanation. Metabolic syndrome is often

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recognized incidentally when horses are presented for other reasons, such as routine health care or other medical problems. In these horses, visible changes in the hoof that are commonly attributable to laminitis (including prominent growth lines, palmar divergence of growth lines, and a convex sole) may be evident in the absence of laminitic pain or any history of laminitis or lameness. There are minimal hematological changes in horses affected with metabolic syndrome (unless laminitic pain is prominent). Abnormal results of routine serum biochemical profiling might include a slight-to-moderate elevation in the glucose and triglyceride concentrations.

ENDOCRINE TESTS

Fasting serum insulin concentration is invariably elevated (>300 pmol/L) in horses affected with the metabolic syndrome; this condition has in both horses and in human beings also been referred to as "hyperinsulinemic syndrome" in the past. Insensitivity to insulin represents one of the most important underlying aspects of the pathogenesis of metabolic syndrome and affected animals are viewed as being under the influence of a state of an "insulin-counter-regulatory overdrive": multiple hormones and fatty acids working together to cause insulin resistance, hypertension, and dyslipidemia. Although the extent to which hypertension and dyslipidemia play a role in equine patients is currently unknown, insulin resistance

is often marked. It is reasonable to suspect that a role for fat ("lipotoxicity") in the pathogenesis of metabolic syndrome in horses might be less than its human counterpart because the equine diet normally contains so little (<2%) fat (compared with the human diet). The effectiveness of insulin in the patient's body can be safely tested in horses by performing an intravenous glucose tolerance test (IVGTT), as described by Garcia and Beech (1986). In the IVGTT, the disposition of an intravenously-administered bolus of glucose is measured over time in the fasted patient. In the healthy state (with respect to insulin sensitivity), the blood glucose concentration should return to baseline within 1 to 2 hours. The presence of glucose intolerance (insulin insensitivity) is suggested when the blood glucose is still elevated after 3 hours post-administration. Blood cortisol concentration is not elevated in metabolic syndrome and results of a dexamethasone suppression test are normal. Although results of spot testing T3 and T4 might yield slightly low values (hence the tendency to diagnose "hypothyroidism" in these cases), results of either TRH or TSH stimulation tests (appropriate testing for thyroid gland function) are normal and thyroid glands from horses affected with metabolic syndrome are normal at necropsy. Further evidence that this condition is NOT hypothyroidism is garnered from the observation that experimentally-induced hypothyroidism (thyroidectomy) does not cause either obesity or laminitis in

horses.

DIAGNOSIS OF METABOLIC SYNDROME

At the present time, the diagnosis of metabolic syndrome must be based on the physical characteristics of mature horses and is, indirectly, supported by demonstrating the presence of hyperinsulinemia and glucose intolerance (using IVGTT). When necessary, other endocrinological conditions should be ruled out using appropriate diagnostic tests (dexamethasone suppression test, TRH-stimulation test).

PATHOGENESIS OF METABOLIC SYNDROME

The pathogenesis of metabolic syndrome in both human and equine patients is currently incompletely understood. Obesity represents an important predisposing condition in both species. Certainly, there also exist underpinnings of genetic susceptibility. The inappropriate accretion of excessive adiposity in susceptible individuals leads directly to an insulin refractory state. Interestingly, it is becoming clear that adipocytes (certain classes) are not simply repositories of stored energy. Some types of adipocytes produce hormones that, in conditions of sufficient adiposity, may exert actions throughout the body. Specifically, various hormones produced by certain types of adipocytes interfere with the molecular action of insulin in insulin-sensitive tissues. One of these hormones is resistin-it is named for the fact that it causes insulin

Perturbations in other aspects of the endocrine system may be occurring simultaneously but the basic premise is adipocyte-driven insulin insensitivity.

Coming Conferences *We'll See You There!*

Colorado State Annual Conference
Fort Collins, CO
Jan 10-12

Missouri VMA
Osage Beach, MO
Jan 16-18

Events of Note

Drinks & Hors d'oeuvres
Abaxis will be hosting an evening hospitality event for old friends and new at both the North American and Western Veterinary Veterinary Conferences.

Please be sure to stop by our booth early in the show to get your FREE tickets!!

North American Veterinary Conference
Orlando, FL
Jan 18-21

Michigan VMA
Lansing, MI
Jan 22-25

Oklahoma VMA
Tulsa, OK
Jan 23-24

Indiana VMA
Indianapolis, IN
Jan 30-31

Local Abaxis Representatives are available to present a one-hour, RACE accredited, presentation on the topic of in-clinic wellness programs and diagnostic testing for local veterinary meetings.

To request a speaker, or support,

Minnesota VMA
Bloomington, MN
Feb 5-7

Louisiana VMA
Layette, LA
Feb 5-7

Western Veterinary Conference
Las Vegas, NV
Feb 15-18

MidWest Veterinary Conference
Columbus, OH
Feb 26-29

at your event, please contact your regional sales director (contact information available in this newsletter or on our website at: www.abaxis.com.)

VetScan® News & Special Offers

VetScan Summer 2004 Avian-Exotic Externship

Abaxis is proud to partner with Dr. Don Harris and Avian & Exotic Animal Medical Center (Miami, FL) to sponsor a 90-day externship in avian and exotic medicine beginning June 2004.

For additional information and applications visit our website:

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NEW VetScan Message Boards

We will be introducing a new VetScan message board on our website beginning January 2004.

You will be able to post and receive response to clinical and practice management queries of all kinds at: www.abaxis.com

We will also be launching a dedicated Message Board for VetScan queries on the Veterinary Information Network early in 2004.

In Your Opinion

We will be discontinuing the *In Your Opinion* feature of VetCom primarily as a result of our two new message boards which we hope will not only serve to answer queries sent in, but also as a forum to discuss and share opinions regarding relevant veterinary issues of the day.

Abaxis Contact Information

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All new VetScan inquiries received by December 15, 2003 will be entered to win a trip for two to NAVC.

Winner will receive 2 RT airline tickets, 3 nights double-occupancy lodging in Orlando and a full DVM re-registration.

Send your inquiries to:
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To read more about our new Message Boards, refer to the *VetScan News and Special Offers* section, above.

Thanks to all who have shared their opinion in the past, we look forward to your future interest on various topics.

Come See Us at NAVC

The North American Vet Conference is a big event for us! Stop by to see our products, talk about future plans and visit with our booth mascot!

Booth 807-811

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user thoughts on
VetScan

"This machine is amazing! I am currently using it to analyze chemistries for both clinical cases and research samples. The machine is fast and accurate! The small volume of blood required for testing makes it possible to collect samples from small amphibians, reptiles, and birds that in the past we could not evaluate!"
Mark A. Mitchell DVM, MS, PhD
Assistant Professor, Zoological Medicine, Louisiana State University

resistance. It remains to be seen whether resistin plays a role in metabolic syndrome in horses. Not all adipocytes are similar with respect to their propensity to produce hormones. In the human species, it is omental (intra-abdominal) adipocytes that appear to be important in this regard. Those people that tend to develop omental obesity ("apple-shaped") are at substantially greater risk for developing insulin insensitivity and its concomitant health problems than those people that preferentially develop subcutaneous ("pear-shaped") obesity. Whether there is a difference between omental and subcutaneous adipocytes in the equine species remains to be determined.

The acquisition of adipocytes is primarily a function of dietary intake (with respect to energy requirements) and genetic factors. Too much energy in the diet (coupled with too little exercise) leads to obesity. However, situations associated with glucocorticoid (GC) excess also tend to preferentially "activate" the omental-type (endocrinologically-active) adipocytes in the body. For example, a well-recognized clinical feature of Cushing's syndrome is the acquisition of omental and subcutaneous fat. The exact mechanism by which GC stimulate the proliferation of active adipocytes is not well understood. It is believed that GC may stimulate proliferation of latent adipocyte progenitors and their differentiation into omental-type, hormone-secreting adipocytes. In this regard, there has been much recent interest focused on the role of stress in the pathogenesis of metabolic syndrome in people. It is unknown whether a similar equine situation exists (GC excess leading to metabolic syndrome). However, horses that survive protracted stress (painful chronic laminitis) are often compromised from a whole-body perspective-these horses tend to be thin and fail to shed their hair-coat appropriately-we have hypothesized that metabolic syndrome may arise in horses that have been subjected to and survived considerable stress-these horses may not be "obese" when presented for examination. A central and essential key to the pathogenesis of metabolic syndrome appears to be both the presence of either excessive numbers (obese individual) or relatively increased activity of (stress-associated, not necessarily obese) omental-like adipocytes and the development of insulin resistance. Perturbations in other aspects of the endocrine system may be occurring simultaneously but the basic premise is adipocyte-driven insulin insensitivity.

MANIFESTATIONS OF INSULIN RESISTANCE

Development of an insulin refractory state potentially leads to numerous diverse clinical and pathological consequences. In human patients, well-recognized clinical complications of persistent and severe insulin insensitivity include heightened risk for developing type-2 diabetes mellitus, hypertension, atherosclerosis, and cardiovascular disease. Specific diabetic complications include myocardial infarction, peripheral neuropathies, nephropathies and

retinopathies. Insulin resistance leads to type-2 diabetes only if there is an inability of pancreatic B-cells to compensate with increased insulin production (hyperinsulinemia). Although the majority of obese people and horses are insulin resistant, only a small proportion of these individuals will develop overt diabetes. The risk for development of overt diabetes (severe hyperglycemia and inappropriately low insulin) in horses affected with the metabolic syndrome appears to be very low-it is a rare condition in this species. As a species, the horse appears very capable of maintaining insulin production in the face of insulin insensitivity. It is possible that the relatively low fat content of the equine diet contributes to the low incidence of complicating diabetes in this species. Alternatively, the fact that horses do not live so long as humans might also explain the comparatively low incidence of diabetes (type-2 diabetes typically arises after 40 years of age in susceptible human patients).

Other tissues, that are not dependent on insulin for glucose uptake, are subjected to relatively high levels of glucose during periods of insulin insensitivity. Of these tissues, endothelial cells are particularly susceptible to the effect of relative glucose excess (known as "glucotoxicity").

Substantial evidence exists to implicate a central and critical role for endothelial dysfunction in the pathogenesis of vascular complications attributable to insulin insensitivity. Abnormalities in endothelial function have been directly attributed to the exposure of blood vessels to only moderate levels of hyperglycemia. Moreover, abnormalities in endothelial function can be demonstrated before the development of histologically-evident atherosclerosis in experimental diabetic states.

Several mechanisms in which excessive glucose leads to widespread endothelial dysfunction have been demonstrated. Increased glucose availability leads to an overall reduction in endothelial-derived nitric oxide (NO) activity and increased expression of endothelin-1 (ET-1). The combination of reduced NO and enhanced ET-1 production leads to a relatively increased state of vasospasticity because NO and ET-1 represent the two most potent endothelium-derived vasorelaxing and vasoconstricting factors, respectively. In addition to the effect on endothelial regulation of underlying vascular tone, hyperglycemic states also tend to cause endothelial cells to be transformed into a relatively pro-coagulative state.

Effect of chronic hyperglycemia on endothelial cell function

Endothelial cells produce a broad array of molecular signals that serve to regulate underlying vascular smooth muscle tone.

Exposure of endothelial cells to hyperglycemia results in alterations in the production of endothelial-derived signals that lead to increased vasospasticity (interaction between endothelial cells and underlying vascular smooth muscle) and attenuation of

anti-thrombotic factors (interaction between endothelial cells and the blood). Although complete understanding of endothelial dysfunction as a result of hyperglycemia is currently lacking, it appears that intracellular generation of oxygen-derived free radicals plays a crucial role. Hyperglycemia leads to enhanced production of oxygen-derived free radicals in endothelial cells and increased expression of endothelial NO synthase (eNOS, the enzyme responsible for production of NO). Superoxide radicals react with NO resulting in production of peroxynitrite, a potent oxidant, and inactivation of NO.

Peroxynitrite stimulates arachidonic acid metabolism and lipid peroxidation. Both cyclo-oxygenase (COX) inhibitors and thromboxane A_2 receptor antagonists have been shown to restore endothelial-dependent vasorelaxation in the diabetic state implying that a significant component of the relative vasospasticity is attributable to the genesis of contractile prostanoids. Similarly, treatment with anti-oxidants, such as superoxide dismutase and vitamin C, has been shown to improve endothelial-dependent vasodilatation in patients and animal models of diabetes. Therefore, although the net production of NO (potent endothelial-derived vasodilator) is increased as a result of hyperglycemia, the simultaneous generation of oxidants acts to neutralize NO and cause enhanced vasospasticity as a result of COX-derived vasoconstrictive prostanoids. It is clear that oxidative stress represents an important contributing factor for the pathogenesis of the impairment of endothelium-dependent vasorelaxation seen in metabolic syndrome.

Abnormalities of coagulation in chronic hyperglycemia

Chronic hyperglycemia is associated with the development of a relatively procoagulant state in metabolic syndrome and in diabetic patients. This procoagulant state is attributable to abnormalities in platelet function, vascular endothelium, and the circulating concentrations of lipid and fibrinolytic factors. In diabetic patients, there tends to be an increase in the number of procoagulation factors such as plasminogen activator inhibitor 1, von Willebrand's factor, fibrinogen, factor VII, factor VIII, and thrombin-antithrombin complexes. These factors promote the survival of a provisional clot matrix when fibrinogen is converted to fibrin at the site of endothelial injury. Increased levels of circulating lipoprotein-a are associated with delayed thrombolysis in diabetic patients. Factors such as antithrombin III, protein S, and protein C, that normally act to attenuate and restrict clot formation, are decreased in diabetic patients. Both platelet aggregability and adhesiveness are

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increased in affected individuals. Platelets are also characterized by an increased capacity for the production of vasoconstrictor prostanoids, decreased vasodilator prostanoid (prostacyclin) production and attenuated capacity to produce NO. Production of NO, thrombomodulin, heparan sulfate proteoglycans, and prostacyclin, normally serve to maintain the antithrombotic phenotype of endothelial cells in the healthy state. In metabolic syndrome, diminished release of NO and prostacyclin and increased expression of procoagulant activity and ET-1 by endothelial cells tend to promote a relatively coagulant state. In summary, conditions associated with the development of insulin insensitivity and glucose intolerance lead to multiple diverse changes in the regulation of hemostasis that tend to promote a pro-coagulative state in obese people and horses.

METABOLIC SYNDROME AND GLUCOCORTICOIDS

As noted above, situations associated with GC excess (stress) may stimulate the genesis of omental-type (endocrinologically-active) adipocytes and lead to metabolic syndrome. Interestingly, these "active" adipocytes also contain the enzyme type-1 11beta-hydroxysteroid dehydrogenase (11betaHSD-1). This enzyme is able to convert circulating cortisone (plentiful inactive metabolite) to cortisol (active glucocorticoid). This production of cortisol occurs locally and exerts paracrine and autocrine influences on cells in-especially-the omental fat deposits. Therefore, these adipocytes-by virtue of 11betaHSD-1-tend to maintain and perpetuate themselves. The extent to which omental 11betaHSD-1-generated cortisol

exerts effects in the body as a whole remains to be seen. New strategies aimed at inhibiting omental 11betaHSD-1 are believed to be potentially useful for the management of metabolic syndrome.

TREATMENT OF METABOLIC SYNDROME

Treatment of metabolic syndrome should primarily be directed at reversal of obesity. The presence of 11betaHSD-1 in omental adipocytes (facilitates perpetuation of this phenotype) represents a challenge and warrants strict adherence to both appropriate dietary restriction and increased exercise. Affected laminitic horses should not be exercised until the laminitis problem has been satisfactorily resolved. It is strongly recommended that dietary fat should be minimized (avoidance of fat-enriched rations for "old" horses). There is some evidence that anti-oxidant strategies might be beneficial-vitamin E can safely be administered to horses at high levels (10,000 units, PO/day). Chromium supplementation has been reported to improve insulin sensitivity in other species but in one equine study, orally-administered chromium L-methionine failed to improve insulin sensitivity in old mares. Further investigation regarding demonstration of any therapeutic value for either chromium, magnesium, or vanadium supplementation for insulin insensitive horses is warranted. Thiazolidinedione drugs increase insulin sensitivity, but their use in the equine metabolic syndrome is only speculative at present. It is recommended that prevention of obesity, especially in those breeds in which metabolic syndrome appears to be common, represents the best advice that is available. The common practice of feeding young and inactive horses excessive quantities of grain should be discouraged.



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www.abaxis.com

REFERENCES

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2. Garcia, MC, Beech, J: (1986) Equine intravenous glucose tolerance test: Glucose and insulin response of healthy horses fed grain or hay and of horses with pituitary adenoma. *Am J Vet Res* 47, 570-572.

Be sure to catch the third and final installment on the topic of equine hypothyroidism in our next issue of VetCom.