Iatrogenic equine
metabolic syndrome in thoroughbred horses

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Summaries

Reasons for performing study: Equine metabolic syndrome (EMS) is a cluster of problem that includes obesity, insulin resistance and laminitis. In EMS peripheral adipocytes synthesize adipokines which are analogous to cortisol, resulting in Cushing syndrome like-signs and insulin resistance. The used of dexamethasone and triancinolone is very common and not permitted.

Hypothesis or Objectives: The objective of this study was to describe metabolic syndrome iatrogenic in Thoroughbred horses.

Methods: Were studied 22 Thoroughbred horses (12 female and 10 male), between 2-5 years old, in the national race Track "La Rinconada" Caracas-Venezuela. All equine were euthanized and study by necropsy. Samples were collected from the adrenal glands, gastric mucosa, pancreas, kidneys, liver, spleen, lungs, heart and adenohypofisys. Tissue sections were prepared and stained with Hematoxilin & Eosin (H&E) for light microscopy.

Results: Clinical signs were polyury, polydipsy and secondary diabetes mellitus, recurrent infection, lethargie, laminitis and weight loss syndrome. Were isolates of recurrent infection: *Salmonella sp.*, *E. coli*, *Streptococcus* sp, *Staphylococcus*, *Enterococcus faecalis* and *Enterobacter cloacae*. Necropsy revealed: weight loss, loss fatty subcutaneous, xantomathosis of subcutaneous tissue. Abscess in coxal tuberous, facial and shoulder region. Liver was swollen, friable and icteric. Renal cortical and papillary necrosis. Equine gastric ulcer syndrome severed. Liver with periacinar necrosis with a prominent acinar pattern and fatty degeneration severed. Necrosis and vacuolar (glycogen) degeneration islets of langerhans, fibrosis and chronic. Renal cortical and medullary necrosis, acute tubular necrosis and glycogen nephrosis, glomerulonephritis membranous. Hemorrhages in adrenal cortex and atrophy cortical.

Conclusions: These results suggest a iatrogenic EMS in Thoroughbred associated with overdose and chronic dexamethasone and triancinolona.

Potential relevance: This article is a clinical study, laboratory, bacterial, macroscopic and histopathological describing the clinical pathologic presentation of metabolic syndrome pathological in Thoroughbreds horses associated with overdose and chronic dexamethasone and triancinolona.

Keys words: Equine, metabolic, Thoroughbred, iatrogenic.

Introduction

The term metabolic syndrome (MS) refers to a clustering of risk factors of metabolic origin that promote the development of cardiovascular disease and type 2 diabetes. Metabolic syndrome includes such pathological factors as insulin resistance, hyperinsulinemia, abdominal obesity, impaired glucose tolerance, type 2 diabetes, microalbuminuria, high level of triglycerides, low level of HDL cholesterol, elevated blood pressure, and proinflammatory and prothrombotic state (Pacholczvk et al 2008). Equine metabolic syndrome (EMS) is a cluster of problem that includes obesity, insulin resistance and laminitis. In EMS peripheral adipocytes synthesize adipokines which are analogous to cortisol, resulting in Cushing syndrome like-signs and insulin resistance. In Venezuela phenylbutazone and furosemide only are permitted in the racecourse of Thoroughbred horses. The used of dexamethasone and triancinolone is very common in horses and not permitted in national race trak from Venezuela. Certain management practices tend to promote the development of obesity (metabolic syndrome) in mature horses as they enter their teenage years. These manage-

ment practices include the provision of starch-rich (high glycemic index) and fat-supplemented rations to healthy horses that are relatively inactive. Some horse breeds and ponies appear to be genetically predisposed to metabolic syndrome. The accretion of intra-abdominal adiposity by equids is associated with the development of insulin insensitivity (hyperinsulinemia), glucose intolerance, dyslipidemia, hypertension, and insidious-onset laminitis (Johnson 2002; Eustace 2002). Omental adipocytes are metabolically active, secreting free fatty acids and hormonally active mediators including cortisol, leptin, and resistin that might contribute to persistence and worsening of insulin refractoriness and the obese phenotype. We have hypothesized that obesity-associated laminitis arises as a consequence of vascular changes and a hypercoagulable state, similar to the development of atherosclerosis in human type 2 diabetes (Johnson 2002). Several molecular mechanisms that might serve to explain the development of insulin insensitivity as a result of excessive adiposity have been incriminated (Johnson 2002). Obesity, insulin resistance, hyperinsulinemia and hypertriglyceridemia are components of an equine metabolic syndrome phenotype associated with increased laminitis risk in horses. Links between these conditions and laminitis must still be elucidated, but human medicine provides candidate mechanisms for future study, including inflammation associated with obesity, vascular compromise induced by insulin resistance, and endothelial dysfunction (Geor and Frank 2009). Clinically affected horses range in age from 6 to 20 years, but rarely are these horses presented initially as geriatric horses, unless undiagnosed until this time. Breed predilection has been observed and has been reported for some pony breeds, domesticated Spanish mustangs, Peruvian Paso's, Paso Fines, European Warmbloods, American Saddlebreds, and Morgan Horses. One common similarity among affected horses is a tendency for obesity; specific locations of fat deposition include crest of the neck, over the gluteus region, and in geldings commonly the prepuce is quite thickened with adipose tissue. Affected female horses are noted for their difficulty in being successfully bred and demonstrate abnormal ovarian cycling activity. Managers of affected horses describe these horses to "live on air" and in many cases this is despite a significant effort implemented to try to improve the horses' body condition. Upon examination of these horses, either with an ultrasound or during exploration of the peritoneal cavity significant intraabdominal fat is observed. In many cases, the presenting complaint includes a history of laminitis, many clinicians have observed the strong association between the development of laminitis in horses with EMS. The objective of this study was to describe metabolic syndrome iatrogenic in Thoroughbred horses.

Material and methods

Animals: Were studied 22 Thoroughbred horses (12 female and 10 male), between 2-5 years old, in the National Race Track "La Rinconada" Caracas-Venezuela.

Clinical signs: were polyury, polydipsy, secondary diabetes mellitus, recurrent infection of skin, lethargie, laminitis and weight loss syndrome (Figure 1). All equine were treatment with dexamethasone (2,2 mg/kg IA weekly for 2 months) and triamcinolone (0,09 mg/kg IM weekly for 2 months).

Hematological and Biochemistry: Bloods of sample were colleted ante mortem (Aluja and Constantino 2002). Samples were process to measure with automatic prosecution equipment: Hemoglobin g/L, Hematocrit %, Protein g/L, Leucocytes x10^9 /L. Urea Nitrogen mmol/L, Creatinine µmol/L, Glucosa mmol/L, cholesterol mmol/L, Cortisol nmol/L, Bilirrubin Total µmol/L, Unconj µmol/L, Conj µmol/L. Alkaline phosphatase U/L, Lactate dehydrogenase U/L, Sorbitol dehydrogenase U/L, Creatin Phosphokinase U/L, Transaminases Aspartate amino U/L, Alanine amino UL, Albumin and Globulin.

Necropsy and histology: All equine were euthanized and study by necropsy (Aluja and Constantino 2002). Samples of tissue were collected from the adrenal glands, gastric mucosa, pancreas, kidneys, liver, spleen, lungs, heart, skin and adenohypofisys (Aluja and Constantino 2002).. Tissue sections were prepared and stained with Hematoxilin & Eosin (H&E) for light microscopy (Banks 1996)

Culture: Were isolates of recurrent infection: Salmonella sp., E. coli, Streptococcus sp, Staphylococcus, Enterococcus faecalis and Enterobacter cloacae. Antibiogram revealed whose resistance to gentamicin, ciprofloxacin and nalidixic acid.

Results

Necropsy: revealed weight loss, loss fatty subcutaneous, xantomathosis of subcutaneous tissue (Figure1). Abscess in coxal tuberous, facial and shoulder region. Multiples hemorrhages in the adrenal cortex (Figure 2). Liver was swollen, friable with fibrosis chronic and icteric. Multifocal necrotic areas were present in the other lobes (Figure 8). Renal cortical and papillary necrosis, acute tubular necrosis (Figure 4). Nine equine (female) presented pyelonefritis abscess and cystitis. Spleen presented severed congestion, hemorrhage. Equine gastric ulcer syndrome severed and ten with colitis chronic (Figure 6). Edema and hemorrhage pulmonary. Petechiae epicardial hemorrhage. Two horses with epicardial abscess. Severe laminitis chronic were observed in all cases with the distal phalanx is torn from the inner hoof wall cells of the lamellar epidermis survive, proliferatite to form the weak, flaky lamellar wedge. The hoof distal phalangeal bond had weakened and the distal phalanx had descended into the hoof capsule. Acrescent-shaped zone of necrosis. Osteomyelitis were observed in 16 equine.

Histology: Liver with periacinar necrosis with a prominent acinar pattern and fatty degeneration severed (Figure 9). Centre-acinar necrosis and billirubin cluster. Necrosis and vacuolar (glycogen) degeneration islets of langerhans, fibrosis and chronic. Renal cortical and medullary necrosis, acute tubular necrosis, degeneration vacuolar and glycogen nephrosis, glomerulonephritis membranous (Figure 5). Hemorrhages in adrenal cortex, capsule thickening and atrophy cortical with coagulation necrosis of zona glomerulosa, coagulation necrosis focal zona fasciculata and coagulation necrosis, congestion of the zona reticularis (Figure 3). Spleen germinal center development within the lymphoid follicles should be noted as decreased. Reactive extramedullary hematopoiesis may be seen in conjunction with conditions that

target the destruction of lymphocytes. Decreased cellularity of the lymphoid follicles, marginal zone and red pulp region were presented. Chronic gastritis surface, erosion focal and hyperkeratosis infiltrated of lymphocytes in the lamina propria (Figure 7). Chronic colitis lymphoplasmocitic. Laminitis and osteomyelitis were showed cause failure of the hoof-distal phalanx bond the epidermal lamellae are stretched beyond their normal limits and significant epidermal lamellar necrosis.

Hematology and biochemistry: value average were Hemoglobin 52-60 g/L, Hematocrit 30-28%, Protein 25-32 g/L, Leucocytes 5,3-6,2 x 10^9/L. Urea Nitrogen 19-21 mmol/L, Creatinine 125-130 µmol/L, Glucosa 7,27-8,8 mmol/L, cholesterol 4,7-5,4 mmol/L, Cortisol 450-520 nmol/L, Bilirrubin Total 25,2-29,5 µmol/L, Unconj 16,6-18,2 µmol/L, Conj 9,6-11,3 µmol/L.   Alkaline phosphatase 61,0 -62 U/L, Lactate dehydrogenase 17,7-18,1 U/L, Sorbitol dehydrogenase 2,2-3,6 U/L, Creatin Phosphokinase 46,4-48,1 U/L, Transaminases Aspartate amino 167,2- 170 U/L, Alanine amino 3,8-4,7 UL. Albumin 22-26 g/L, Globulin 21-25 g/L.

Culture: Were isolates of recurrent infection: *Salmonella sp., E. coli, Streptococcus* sp, *Staphylococcus, Enterococcus faecalis* and *Enterobacter cloacae*. Antibiogram revealed whose resistance to gentamicin, ciprofloxacin and nalidixic acid.

Figure 1

Equine with iatrogenic equine metabolic syndrome with weight loss. Abscess in coxal tuberous, facial and shoulder region and lesion of skin.
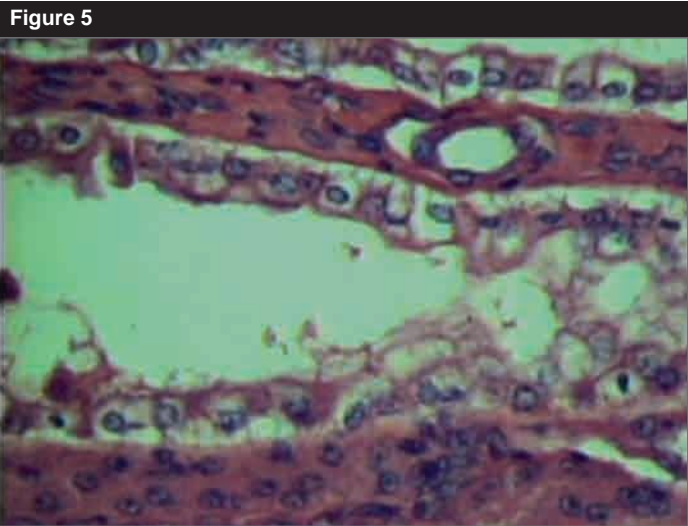
Figure 2

Adrenal glands of equine with atrophic and multiples hemorrhages in the adrenal cortex

Figure 3
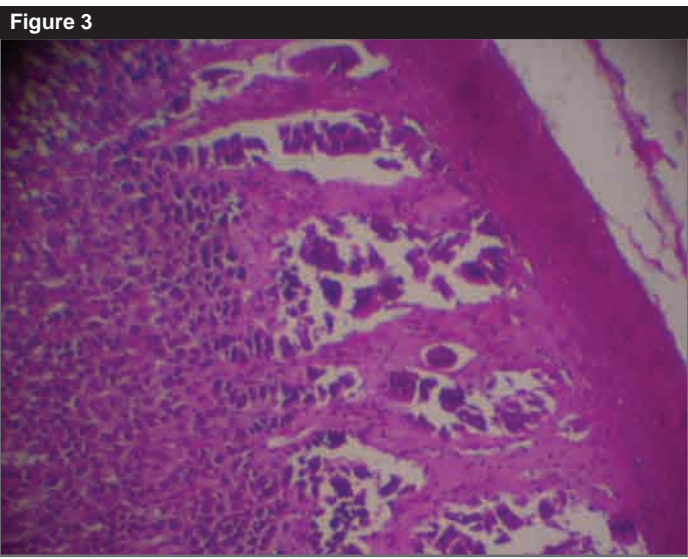
Adrenal glands histology of equine with iatrogenic equine metabolic syndrome showed hemorrhages in adrenal cortex, capsule thickening and atrophy cortical with coagulation necrosis of zona glomerulosa, coagulation necrosis focal zona fasciculata and coagulation necrosis, congestion of the zona reticularis (Hematoxilin & Eosin 10X)

Figure 4

Kydney of equine with iatrogenic equine metabolic syndrome Renal cortical and papillary necrosis, acute tubular necrosis.

Figure 5

Kidneys histology of equine with iatrogenic equine metabolic syndrome acute tubular necrosis and severed degeneration vacuolar. (Hematoxilin & Eosin 20X).
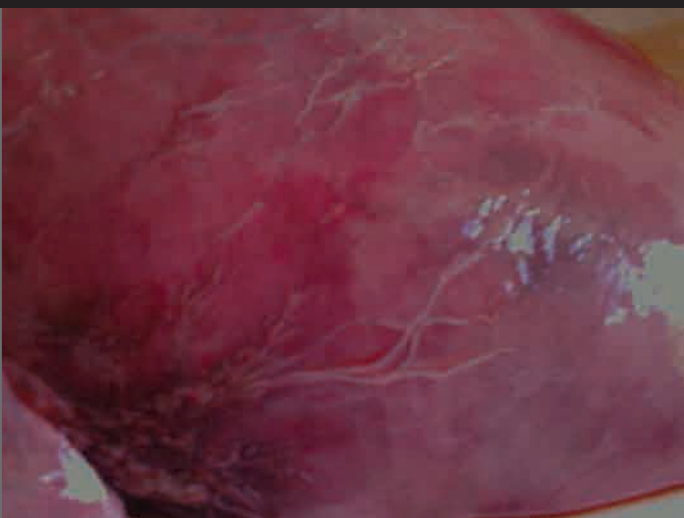
Figure 6

Gastric mucosa of equine with iatrogenic equine metabolic syndrome with equine gastric ulcer syndrome severed, multiple ulcers and focal erosion with exposition of lamina propria
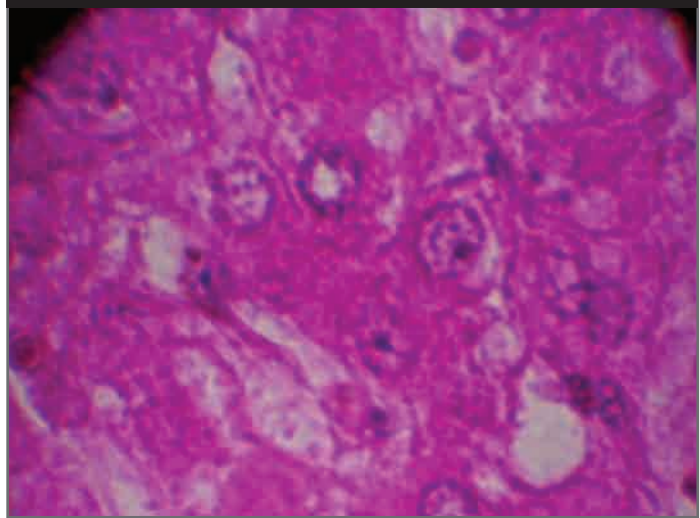

Figure 7
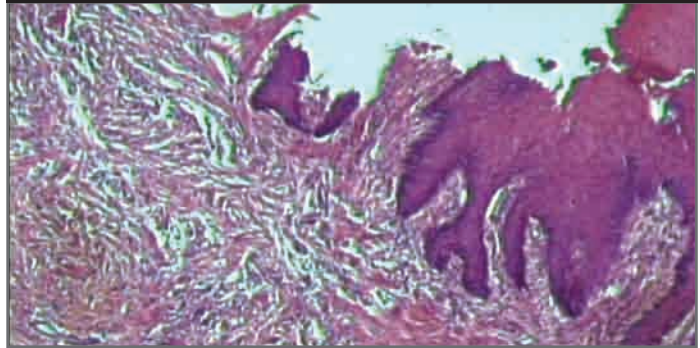
Gastric mucosa histology of equine with iatrogenic equine metabolic syndrome showed chronic gastritis surface, focal ulcer, erosion focal and hyperkeratosis infiltrated of lymphocytes in the lamina propria. (Hematoxilin & Eosin 10 X).

Figure 8

Liver of equine with iatrogenic equine metabolic syndrome, swollen, friable with fibrosis chronic and icteric. Multifocal necrotic areas were present in the other lobes

Figure 9

Liver histology of equine with iatrogenic equine metabolic syndrome with periacinar necrosis with a prominent acinar pattern and fatty degeneration severed (Figure 9). Centre-acinar necrosis and billirubin cluster (Hematoxilin & Eosin 20X).

Discussion

These results suggest of an iatrogenic EMS in Thoroughbred. The metabolic syndrome is a common and complex disorder combining obesity, dyslipidemia, hypertension, and insulin resistance. It is a primary risk factor for diabetes and cardiovascular disease. We showed for the first time that the metabolic syndrome is associated with a higher fraction of oxidized LDL and thus with higher levels of circulating oxidized LDL. Hyperinsulinemia and impaired glycaemic control, independent of lipid levels, were associated with increased in vivo LDL oxidation, as reflected by the higher prevalence of high oxidized LDL. High levels of oxidized LDL were associated with increased risk of future myocardial infarction, even after adjustment for LDL-cholesterol and other established cardiovascular risk factors (Jubb et al 1984; Pacholczvk et al 2008). Situations of glucocorticoid excess such as stress or pituitary dysfunction may stimulate the production of hormonally active adipocytes that lead to metabolic syndrome (Botana et al 2002; Eustace 2008;

Hardman J and Limbird 2003). Interestingly the active adipocytes contain an enzyme called 11beta-hydroxysteroid dehydrogenase type-1 (11betaHSD-1). This enzyme has the critical function of turning inactive cortisone into active cortisol which is the active glucocorticoid. This production of cortisol occurs locally and exerts both paracrine (local) and autocrine (back to the originating cell) effects. Therefore, these adipocytes, due to the presence of 11betaHSD-1 have the capacity to maintain and perpetuate themselves. The overall extent to which 11betaHSD-1 generated cortisol exerts effects in the body as a whole, remains to be determined. New strategies aimed at inhibiting omental 11betaHSD-1 production are believed to be potentially useful for the management of metabolic syndrome. Moreover, although the effects of GC are apparent it is important to recognize that this is not a condition of abnormal adrenal function. Even though glucocorticoid are involved in the pathogenesis of disease, since adrenal function is normal, diagnostic assays designed for detection of altered circulating cortisol levels are within normal limits; subsequently,

therapeutic strategies aimed at treating pituitary dysfunction will have no effect on horses with EMS unless there is concurrent pituitary dysfunction present. Studies are now required to determine the exact mechanisms responsible for the increased predisposition to laminitis observed in horses with equine metabolic syndrome (Geor and Frank 2009). In Venezuela is a very common the chronic treatment of dexamethasone and triamcinolone in Thoroughbreds. Cumulative doses of dexamethasone and triamcinolone induce EMS, possibly associated with training, and career management practices. The lesions, necropsy and histology observed in this study are similar to the EMS, with the exception of obesity (Donald 1996; Jubb et al 1984). The multiple organ failures complicating the clinical and compromises the horse's life. Immunosuppression appears to be one of the consequences that lead to chronic and recurrent in these horses, not responsive to therapy. This syndrome leads to huge economic losses each year in the equine industry. In conclusion our reported a iatrogenic equine metabolic syndrome in Thoroughbred horses from Venezuela associated with overdose and chronic dexamethasone and triancinolona.

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