# Characterization of hypertriglyceridemia and response to treatment with insulin in horses, ponies, and donkeys: 44 cases (1995–2005)

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**Objective**—To characterize signalment, clinical signs of disease, and clinical response to insulin in equids with hypertriglyceridemia.

**Design**—Retrospective case series.

**Animals**—20 horses, 17 ponies, and 7 donkeys with hypertriglyceridemia.

**Procedures**—For analysis of medical record data, horses, donkeys, and ponies with multiple serum or plasma triglycerides measurements were separated into groups. Hypertriglyceridemic equids that were (HT-I; n = 14) or were not (HT-N; 10) treated with insulin consisted of equids with an initial triglycerides concentration > 44 mg/dL but < 500 mg/dL. Equids with an initial triglycerides concentration > 500 mg/dL, all of which were treated with insulin, constituted the lipemic group (LIP-I; 20). Each group included a full range of ages. Pretreatment and posttreatment values from serum or plasma biochemical analyses were compared among groups.

**Results**—No age predilection for hypertriglyceridemia was apparent. Of the 29 female equids, only 7 (24%) were lactating or pregnant. Multiple illnesses were diagnosed in hypertriglyceridemic equids, including colitis (14/44; 32%) and colic (9/44; 20%). Many breeds were affected, including 16 (36%) American Miniature Horses and 9 (20%) Arabians or Arabian crossbreds. The mean posttreatment triglycerides concentration was not significantly different from the initial value in HT-N equids (175 vs 125 mg/dL) but was significantly lower than the pretreatment triglycerides concentration in HT-I (252 vs 55 mg/dL) and LIP-I (872 vs 87 mg/dL) equids.

**Conclusions and Clinical Relevance**—Equids of all ages and sexes with various diseases had hypertriglyceridemia. Insulin treatment decreased the triglycerides concentrations in affected equids. (*J Am Vet Med Assoc* 2009;234:915–919)

Hypertriglyceridemia is a life-threatening condition in horses, ponies, and donkeys.[1–4] Left undetected or untreated, hypertriglyceridemia may progress to hepatic lipidosis and liver failure with multisystemic complications.[1] Suspicion of hypertriglyceridemia is important for diagnosis because onset of the condition is insidious, with few specific clinical signs other than general malaise. Suggested predisposing factors include hypophagia, pregnancy, or lactation, most remarkably in obese ponies, American Miniature Horses, or donkeys.[1–6] Hypertriglyceridemia can be complicated by concurrent illness, particularly azotemia, which can inhibit the removal of triglycerides from the bloodstream,[7] whereas excess circulating concentrations of tumor necrosis factor, as occurs with colitis or colic, can increase lipolysis.[2] Activities of lipoprotein lipase and hepatic lipase are higher in hypertriglyceridemic, feed-deprived horses than in fed horses.[8] This suggests that overproduction of triglycerides, possibly complicated by defective catabolism, is the predominant cause of hypertriglyceridemia.[9]

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**Abbreviations**

| | |
|---|---|
| AST | Aspartate aminotransferase |
| BHB | β-Hydroxybutyrate |
| CK | Creatine kinase |
| GGT | γ-Glutamyltransferase |
| HT-I | Hypertriglyceridemic and insulin-treated |
| HT-N | Hypertriglyceridemic and not insulin-treated |
| IQR | Interquartile range |
| LIP-I | Lipemic and insulin-treated |
| NEFA | Nonesterified fatty acids |
| SDH | Sorbitol dehydrogenase |

Research into the pathogenesis of hypertriglyceridemia has revealed that fat mobilization is minimally affected by thyroid gland hormones,[8] whereas lipolysis and ketogenesis increase in horses with hyperadrenocorticism.[10] However, administration of corticosteroid drugs does not increase the severity of hypertriglyceridemia, even when combined with the withholding of feed from affected ponies.[11] The administration or endogenous release of catecholamines, which results in an increase in plasma triglycerides concentrations in camelids[12] and cats,[13] has not been evaluated in equids. Unlike ketonemia in ruminants and camelids, which develops when an animal is in a metabolic negative energy balance,[14,15] ketonemia in equids does not appear to be clinically important.[1–4] Dietary factors can also influence triglycerides

concentration. For example, low blood triglycerides concentrations develop in horses fed high-fat diets because of an increase in lipoprotein lipase activity.[16]

Some researchers have postulated that hyperlipemia is associated with insulin resistance, particularly in obese ponies,[17,18] and that age-related decreases in insulin sensitivity may contribute to a high prevalence of hyperlipemia in older equids.[17] However, in a study[11] of 8 ponies that developed hypertriglyceridemia after feed was withdrawn, 4 ponies had clinically normal insulin responses. Hypertriglyceridemia in a neonatal pony has also been reported,[19] suggesting the contribution of factors other than age-related changes.

Many treatment approaches have been proposed to aid in the resolution of hypertriglyceridemia. Most of them consist of enteral[2,20] or parenteral[1–3,21] nutritional support. Heparin has been used as an adjunctive treatment because of its ability to act as a cofactor for lipoprotein lipase that is bound to the endothelium.[1] Insulin administration decreases the serum or plasma triglycerides concentration in healthy camelids[12] and may have the same effect in camelids with hypertriglyceridemia.[22] To the authors' knowledge, insulin has not been evaluated as a primary means of treating equids with hypertriglyceridemia. Because excess fat mobilization is commonly attributed to insulin resistance, it has been postulated that insulin administration would not result in a reduction of serum triglycerides concentration.[2] However, we are unaware of any scientific reports that substantiate or refute this supposition.

Insulin inhibits fat mobilization by inhibiting the activity of hormone-sensitive lipase and promotes the uptake of triglycerides into peripheral tissues by stimulating the activity of lipoprotein lipase. The purpose of the study reported here was to determine the response of hypertriglyceridemic equids to insulin treatment and to describe the signalment and clinical features of disease in affected horses, donkeys, and ponies. The hypothesis was that insulin administration assists in restoring serum or plasma triglycerides concentrations to within the reference range in equids mildly and severely affected with hypertriglyceridemia.

## Materials and Methods

**Case selection**—Medical records were reviewed to identify horses, donkeys, and ponies that had a serum or plasma triglycerides concentration > 44 mg/dL (reference range, 22 to 44 mg/dL) and were treated at Oregon State University Veterinary Teaching Hospital from 1995 through 2005. Only equids with multiple measurements were included in the study.

**Medical records review**—Information on equids obtained from the records included signalment, pregnancy or lactation status, nature of other disease processes, treatments received and timing of administration, and whether the equid survived to discharge from the hospital. Also recorded were serum or heparinized plasma[a] concentrations of NEFA, triglycerides, cholesterol, BHB, glucose, urea nitrogen, creatinine, and albumin as well as activities of AST, GGT, SDH, and CK. These data were used to characterize hypertriglyceridemia in equids.

Three classifications of equids were established. Hypertriglyceridemic equids with a triglycerides concentration that did not exceed 500 mg/dL were classified as HT-N or HT-I on the basis of whether they had been treated with insulin (which was determined by clinician preference). Equids that had a triglycerides concentration > 500 mg/dL and were treated with insulin were classified as LIP-I. For equids treated with insulin, pretreatment serum or plasma biochemical values were defined as those measured when the equids were first admitted to the hospital, and posttreatment values were defined as the first available values measured after insulin administration. For equids not treated with insulin, values for serum or plasma biochemical analytes that were measured at admission were considered initial values, and subsequent values were defined as the next available serum or plasma biochemical values measured during hospitalization. Sample collection times were based upon clinician preference and the clinical progress of each equid.

**Statistical analysis**—Commercial software was used for all statistical analyses.[b] Clinicopathologic data obtained when the equids were initially admitted to the hospital were compared between those with a triglycerides concentration < 500 mg/dL and those with a triglycerides concentration > 500 mg/dL by use of a Mann-Whitney *U* test. To additionally characterize hypertriglyceridemia, initial clinicopathologic data for equids that did and did not survive to discharge from the hospital were similarly compared. Pretreatment or initial and posttreatment or subsequent biochemical values were also compared between equids classified as HT-N and HT-I by use of the Mann-Whitney *U* test. Pretreatment or initial and posttreatment or subsequent biochemical values in each of the HT-N, HT-I, and LIP-I groups were compared with a Wilcoxon signed rank test. The intervals between determinations of pretreatment or initial and posttreatment or subsequent values were compared via Kruskal-Wallis 1-way ANOVA. A value of $P < 0.05$ was considered significant for all analyses.

## Results

**General characteristics of equids**—From 1995 through 2005, 44 hypertriglyceridemic equids with multiple measurements of serum or plasma triglycerides concentrations were identified. Of these, 20 (45%) were horses, 17 (39%) were ponies, and 7 (16%) were donkeys. Various horse and pony breeds were represented, whereas Miniature Sicilian Donkey was the only donkey breed (**Table 1**). Twenty-nine (66%) equids were female, and 15 (34%) were male. Seven (24%) of the females were pregnant or lactating. Seven equids were < 6 months old, 9 were between 6 months and 3 years of age, 19 were between 4 and 15 years of age, and 9 were > 15 years old.

Several disease states were evident in the hypertriglyceridemic equids. Fourteen had colitis, whereas 9 had classic signs of abdominal pain without fever, low WBC count, and soft fecal consistency (Table 1). Six equids did not have a recorded diagnosis other than hypertriglyceridemia or hyperlipemia.

Ten equids were classified as HT-N, 14 were classified as HT-I, and 20 were classified as LIP-I. Ages of equids in the HT-N group ranged from 4 days to 20 years, ages of those in the HT-I group ranged from 1

month to 23 years, and ages of those in the LIP-I group ranged from 2 days to 22 years. Every group contained pregnant or lactating females except the HT-N group.

**Comparisons among equids**—All 10 equids classified as HT-N survived. Only 1 equid classified as HT-I did not survive, and necropsy revealed it had carcinomatosis. Six equids classified as LIP-I did not survive. Two of these had pituitary adenomas, 2 had hepatic lipidosis and developed neurologic signs, 1 had undergone surgery for colic, and 1 had no other disease state recorded. All of these 6 horses were euthanized after intensive hospitalization at the recommendation of the senior clinician on the basis of poor response to treatment, a grave prognosis, or both.

Equids that survived or did not survive to discharge from the hospital did not differ significantly with respect to serum or plasma biochemical values. When these values were compared between equids with triglycerides concentrations > or < 500 mg/dL, only serum or plasma concentrations of triglycerides, NEFA, and cholesterol were significantly different.

When values for each serum or plasma biochemical analyte obtained when equids were admitted to the hospital were compared between the HT-I and HT-N groups, the only significant difference was that creatinine concentration was higher in the HT-N group than in the HT-I group (**Table 2**). Subsequent values for the HT-N equids and posttreatment values for the HT-I equids were significantly different with respect to concentrations of BHB, urea nitrogen, total bilirubin, and glucose only. There was no significant difference among intervals between determination of initial and subsequent values for the HT-N group (median, 2 days; IQR, 1 to 2 days) and pretreatment and posttreatment values for the HT-I (median, 1 day; IQR, 1 to 2 days) and LIP-I (median, 1 day; IQR, 1 to 2 days) groups.

In the HT-N group, there was a significant decrease in serum or plasma SDH activity and creatinine concentration between initial and subsequent measurement points. In the HT-I group, there was a significant decrease in serum or plasma concentrations of triglycerides, NEFA, BHB, cholesterol, urea nitrogen, and total bilirubin after insulin treatment. In the LIP-I group, there was a significant decrease in serum or plasma concentrations of triglycerides, BHB, cholesterol, urea nitrogen, creatinine, and total bilirubin and CK activity after insulin treatment (**Table 3**).

Table 1—Characteristics of 44 hypertriglyceridemic* equids that were treated with or without insulin at a referral hospital from 1995 through 2005, and for which results of multiple assessments of serum or plasma triglycerides concentrations were available.

| Characteristic | HT-N (n = 10) | HT-I (n = 14) | LIP-I (n = 20) |
|---|---|---|---|
| Breed or type | | | |
| American Miniature Horse | 4 | 4 | 8 |
| Arabian or Arabian crossbred | 2 | 2 | 5 |
| Stock† | 3 | 3 | 1 |
| Miniature Sicilian Donkey | 0 | 3 | 4 |
| Baroque‡ | 1 | 1 | 1 |
| Pony | 0 | 1 | 0 |
| Draft horse | 0 | 0 | 1 |
| Sex | | | |
| Female (not pregnant or lactating) | 5 | 9 | 15 |
| Female (pregnant or lactating) | 0 | 3 | 4 |
| Male | 5 | 5 | 5 |
| Disease states | | | |
| Colitis | 5 | 3 | 6 |
| Colic | 2 | 5 | 2 (1) |
| Unknown | 1 | 2 | 3 (1) |
| Hepatic lipidosis | 0 | 0 | 3 (2) |
| Pituitary adenoma | 0 | 1 | 2 (2) |
| Sepsis or failure of passive transfer | 1 | 0 | 1 |
| Laminitis | 0 | 1 | 0 |
| Peritonitis | 1 | 0 | 1 |
| Carcinomatosis | 0 | 1 (1) | 0 |
| Purpura hemorrhagica | 0 | 0 | 1 |
| Hemolysis | 0 | 0 | 1 |
| Hepatitis | 0 | 1 | 0 |

Values in parentheses indicate the number of equids that did not survive to discharge from the hospital.
*Hypertriglyceridemia was defined as serum or plasma triglycerides concentration > 44 mg/dL (reference range, 22 to 44 mg/dL). †Stock breeds included Quarter Horse, Paint, Mustang, and Appaloosa. ‡Baroque breeds included Lipizzan and Andalusian.

Table 2—Median (IQR) values of initial and subsequent serum or plasma biochemical analytes in HT-N equids (n = 10) and pretreatment and posttreatment serum or plasma biochemical analytes in HT-I equids (14).

| | HT-N | | HT-I | |
|---|---|---|---|---|
| Variable | Initial | Subsequent | Pretreatment | Posttreatment |
| Triglycerides (mg/dL) | 175 (99–347) | 125 (39–265) | 252 (190–423) | 55 (32–68)* |
| NEFA (mEq/L) | 0.78 (0.49–1.00) | 0.73 (0.44–0.91) | 0.59 (0.52–0.96) | 0.33 (0.17–0.35)* |
| BHB (mg/dL) | 1.77 (1.59–2.86) | 2.41 (1.13–3.88) | 2.21 (0.89–4.51) | 0.57 (0.45–0.38)*,† |
| Cholesterol (mg/dL) | 106 (690–115) | 90 (62–107) | 102 (94–130) | 93 (76–108)* |
| Glucose (mg/dL) | 117 (81–149) | 104 (86–116) | 127 (96–140) | 130 (113–189)† |
| Urea nitrogen (mg/dL) | 24.0 (13.0–33.0) | 18.5 (12.0–21.0) | 11.0 (9.8–15.0) | 9.0 (7.5–11.0)*,† |
| Creatinine (mg/dL) | 1.35 (1.10–1.80) | 1.20 (0.90–1.50)* | 0.90 (0.78–1.23)‡ | 0.95 (0.70–1.10) |
| Albumin (mg/dL) | 3.10 (2.10–3.30) | 2.80 (1.90–3.30) | 2.90 (2.10–3.00) | 2.50 (2.00–3.00) |
| Total bilirubin (mg/dL) | 2.80 (1.50–4.10) | 2.10 (1.60–2.50) | 1.9 (1.6–3.38) | 1.15 (0.85–1.60)*,† |
| CK (U/L) | 264 (188–503) | 241 (133–408) | 269 (155–450) | 257 (163–446) |
| GGT (U/L) | 15.5 (12.0–22.0) | 15.0 (10.0–18.0) | 18.0 (10.8–37.8) | 17.0 (11.0–40.5) |
| AST (U/L) | 349 (178–517) | 272 (203–487) | 303 (237–491) | 311 (250–477) |
| SDH (U/L) | 19.1 (4.1–26.9) | 9.6 (6.2–20.4)* | 10.4 (4.1–10.9) | 7.3 (4.2–11.6) |

*Values are significantly ($P < 0.05$) different between time points within the same group. †Posttreatment value in the HT-I group is significantly ($P < 0.05$) different from the subsequent value in the HT-N group. ‡Pretreatment value in the HT-I group is significantly ($P < 0.05$) different from the initial value in the HT-N group.

Table 3—Median (IQR) values of pretreatment and posttreatment serum or plasma biochemical analytes in 20 lipemic (triglycerides concentration > 500 ng/mL) equids treated with insulin.

| Variable | Pretreatment | Posttreatment | *P* value |
|---|---|---|---|
| Triglycerides (mg/dL) | 872 (731–1,522) | 86 (54–202) | < 0.001 |
| NEFA (mEq/L) | 1.11 (0.80–1.48) | 0.30 (0.17–0.59) | 0.06 |
| BHB (mg/dL) | 2.23 (1.07–6.17) | 0.67 (0.53–1.32) | 0.03 |
| Cholesterol (mg/dL) | 168 (122–198) | 112 (77–165) | 0.004 |
| Glucose (mg/dL) | 141 (100–215) | 146 (120–232) | 0.64 |
| Urea nitrogen (mg/dL) | 20.0 (12.1–24.5) | 12.5 (7.6–14.5) | < 0.001 |
| Creatinine (mg/dL) | 1.20 (0.83–1.58) | 0.90 (0.63–1.40) | 0.02 |
| Albumin (mg/dL) | 2.85 (2.00–3.30) | 2.45 (1.80–2.95) | 0.24 |
| Total bilirubin (mg/dL) | 2.30 (0.85–4.78) | 1.10 (0.80–2.00) | 0.03 |
| CK (U/L) | 418 (278–616) | 347 (202–553) | 0.007 |
| GGT (U/L) | 24.0 (13.0–90.5) | 18.0 (9.8–75.8) | 0.86 |
| AST (U/L) | 442 (304–1,730) | 404 (257–1,247) | 0.42 |
| SDH (U/L) | 5.45 (2.50–9.60) | 6.20 (4.50–7.88) | 0.73 |

A value of $P < 0.05$ was considered significant.

**Treatment of equids**—Equids in the HT-N group immediately received appropriate treatment for their primary disease. Of the 10 equids in that group, 3 received IV nutritional support in the form of dextrose-supplemented fluids (1% to 5% in polyionic fluids administered at a maintenance rate). All equids treated with insulin also received continuous rate infusions of dextrose-containing fluids (1% to 5% in polyionic fluids, administered IV at a maintenance rate) until 24 hours after administration of the final dose of insulin to prevent hypoglycemia. Hypoglycemia was not reported as a complication in these equids.

Most equids received a partial parenteral nutrition–type fluid consisting of amino acids, dextrose, vitamin B complex, and selected electrolytes. Equids were treated for their primary disease state with various combinations of the following types of drugs: anti-inflammatories (flunixin meglumine, ketoprofen, or dimethyl sulfoxide), antithrombotics (heparin or acetylsalicylic acid), antimicrobials (potassium penicillin, gentamicin, amikacin, ceftiofur, ampicillin, oxytetracycline, trimethoprim-sulfamethoxazole, or metronidazole), gastroprotectants (omeprazole, sucralfate, cimetidine, or ranitidine), analgesics (butorphanol or constant rate infusion of lidocaine), prokinetics (erythromycin, metoclopramide, or constant rate infusion of lidocaine), anthelmintics (fenbendazole), and antidiarrheals (enteroadsorbent paste, activated yeast, lactase tablets, or bismuth subsalicylate). All 3 equids treated with heparin were in the LIP-I group.

Suspensions of insulin differed in content throughout the 10 years because of changes in availability and clinician preference. Regular insulin[c] (0.2 U/kg) was administered IV as often as every hour (most commonly every 6 hours) during the initial treatment of severely lipemic equids or equids that did not respond (possibly insulin resistant), in which an immediate effect was desired. Regular insulin was usually discontinued within 24 hours after response to treatment. Ultralente insulin[d] (0.4 U/kg, SC, q 24 h) was also used. Monitoring of serum or plasma glucose concentration was performed every 1 to 6 hours on the basis of clinician preference and dosing schedule.

## Discussion

In the present study, female equids, particularly those that were lactating or pregnant, were overrepresented among hypertriglyceridemic equids; however, equids of all signalments had hypertriglyceridemia. High triglycerides concentration coexisted with a broad range of diseases and not just with those associated with obesity, liver abnormalities, or anorexia. Diseases associated with an injury to the gastrointestinal tract accounted for most illnesses in the hypertriglyceridemic equids. Anorexia associated with these disease states may have contributed to fat mobilization, possibly combined with an increase in circulating tumor necrosis factor[1,2] or other stress hormones, thereby exacerbating lipolysis.

Hypertriglyceridemia was not associated with failure to survive to discharge from the hospital, which suggested that fat mobilization was either a typical metabolic response to disease that resolved with resolution of the primary disease or a treatable condition. Additionally, there was no consistent clinicopathologic evidence of more widespread, systemic dysfunction among lipemic equids that were treated with insulin. However, more equids in the LIP-I group than in the HT-I and HT-N groups failed to survive to discharge from the hospital, so it could be that more severe hypertriglyceridemia results in a greater degree of fat mobilization and vice versa. The lack of an association between high serum or plasma triglycerides concentration and failure to survive may be attributable to the fact that almost all of the nonsurviving equids were euthanized for untreatable primary disease states and not specifically because of treatment failure.

Equids in the LIP-I group had significant decreases in most fat-related serum or plasma biochemical analytes after treatment with insulin. These decreases may have been attributable to insulin administration and were similar to the effects of insulin reported for hypertriglyceridemic camelids.[12,22] However, because there was no untreated control group for comparison with the LIP-I group, this hypothesis could not be evaluated. Serum or plasma concentrations of urea nitrogen and creatinine decreased significantly after insulin treatment, likely because the dehydration status of treated equids had been corrected. Reduction of azotemia could also have contributed to the reduction in serum or plasma triglycerides concentration because uremic compounds reportedly inhibit clearance of triglycerides from the bloodstream.[7] Serum or plasma total bilirubin concentration and CK activity also decreased significantly after insulin treatment to within reference ranges, which was likely attributable to resolution of the cachectic and dehydrated state of treated equids.

Similar to equids in the LIP-I group, those in the HT-I group had significant decreases in values for all fat- and energy-related serum or plasma biochemical analytes after treatment with insulin, with the exception of glucose. For the most part, these effects were not evident in the HT-N equids, despite a slightly longer period of evaluation. The contribution of azotemia to hypertriglyceridemia could not be ruled out in the HT-N equids, but as with the LIP-I equids, the reduction in serum or plasma concentrations of NEFA and BHB after insulin treatment suggested a general inhibition of fat mobilization by insulin.

In the HT-N equids, the only significant changes in serum or plasma biochemical values during the study were a decrease in creatinine concentration and SDH activity. This was likely attributable to resolution of dehydration after treatment with fluids. Because SDH is an

acute mediator of liver cell damage, an increase in SDH activity could have been the result of poor perfusion from dehydration or various insults to the liver; however, values for no other liver enzymes changed significantly after hospitalization, including those that originally exceeded the upper reference limit, so the aforementioned decrease should be interpreted accordingly.

Exogenous insulin administration appeared to aid in clearance of triglycerides from the bloodstream in the 2 treated groups of equids. Although insulin treatment did not affect the likelihood of survival to discharge from the hospital, it appeared to ameliorate the hypertriglyceridemic state, which if left untreated may have adversely affected the likelihood of survival. Because healthy equids have a robust endogenous insulin response to dextrose administration,[23] it is possible that favorable results could have been achieved with dextrose administration alone. However, approximately a third of the equids that were not treated with insulin did have some form of parenteral nutrition, and no significant improvements in serum or plasma biochemical values were detected in that group.

Whether the high triglycerides concentration was a result of or contributed to the other disease states in the equids in the present study remains unknown. The diversity of signalments and concurrent disease states in hypertriglyceridemic equids suggested that determination of blood triglycerides concentration would be a reasonable component of the diagnostic evaluation of any clinically abnormal equid. Equids may benefit from the administration of exogenous insulin during periods of fat mobilization or inhibited fat clearance.

a. Hitachi 717 biochemistry analyzer, Roche Diagnostics, Indianapolis, Ind.
b. SigmaStat, version 2.0, SPSS Inc, Chicago, Ill.
c. Humulin R, Eli Lilly Co, Indianapolis, Ind.
d. Humulin U, Eli Lilly Co, Indianapolis, Ind.

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