A cushingoid pony. Pituitary pars intermedia dysfunction is one of a number of disease processes commonly associated with equine hyperlipaemia. Picture, Dr C. McGowan

Management of equine hyperlipaemia

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EQUINE hyperlipaemia is characterised by abnormalities in lipid metabolism and primarily affects ponies and donkeys. The condition has a high mortality rate of between 60 and 100 per cent, and a reported prevalence of between 5 and 11 per cent in ponies and 18 per cent in donkeys in referral hospital populations. Early recognition of the disease and prompt intervention are vital to improve an animal's chance of survival. This article discusses risk factors and reviews current treatment options for this challenging condition. In view of the poor prognosis, it highlights the importance of client education in disease prevention.

EPIDEMIOLOGY

Ponies (especially Shetland ponies) and donkeys have a significantly higher risk of acquiring equine hyperlipaemia than horses, although the condition has been reported in thoroughbreds, standardbreds, quarter horses and Arabs which have severe concurrent disease.

Females are predisposed to the disease, the risks of which are further increased by pregnancy or lactation due to hormonal changes and greater nutritional demands during this period. There is a positive correlation between body condition score and hyperlipaemia (many animals are fat or obese prior to onset), although anorexia, whether it be forced (eg, in the management of laminitis) or secondary to another condition, is a frequent finding. The author has seen hyperlipaemia in several aged ponies and donkeys with virtually no remaining teeth. While disease is more common in older animals, it has been reported in severely compromised foals, including a congenital case involving a foal born to a hyperlipaemic dam.

A common finding in the history of affected animals is stress immediately prior to the onset of disease. Typical stressors are transportation, a change in management or diet, adverse weather conditions and concurrent disease. An underlying disease process, such as intestinal parasitism, enteritis, colic, intestinal lymphosarcoma, dysphagia, laminitis and pituitary pars intermedia dysfunction (equine Cushing's disease), is reported in approximately 30 to 50 per cent of cases.

Risk factors

Inherent risk factors
- Type of equid
  - Ponies
  - Donkeys
- Sex
  - Females

Other precipitating factors
- Pregnancy and lactation
- Obesity
- Food deprivation
- Concurrent disease
- Stress

PATHOGENESIS

The liver plays a crucial role in the maintenance of energy balance. Under normal metabolic conditions, hepatic glycogen stores form a major source of plasma glucose; however, when energy supply is limited or nutritional demands are increased, glycogen stores become depleted and fatty acids released from adipose tissue become the main source of energy. The mechanism which releases non-esterified fatty acids (NEFAs) from adipose tissue is controlled by an enzyme called hormone-sensitive lipase (HSL). The activity of HSL is inhibited by insulin and glucose and increased by glucagon, which is why HSL is more active during fasting.

The majority of the fatty acids released from adipose tissue are taken up by the liver. Thereafter, they are either:
- Oxidised to acetyl coenzyme A, which is then used in the tricarboxylic acid cycle;
- Used for gluconeogenesis; or
- Esterified to tryglycerides which are stored in the liver or released as very low density lipoproteins (VLDLs).

The lipoproteins produced are cleared from the circulation by the action of the enzyme lipoprotein lipase (LPL) at the capillary endothelium and deposited into

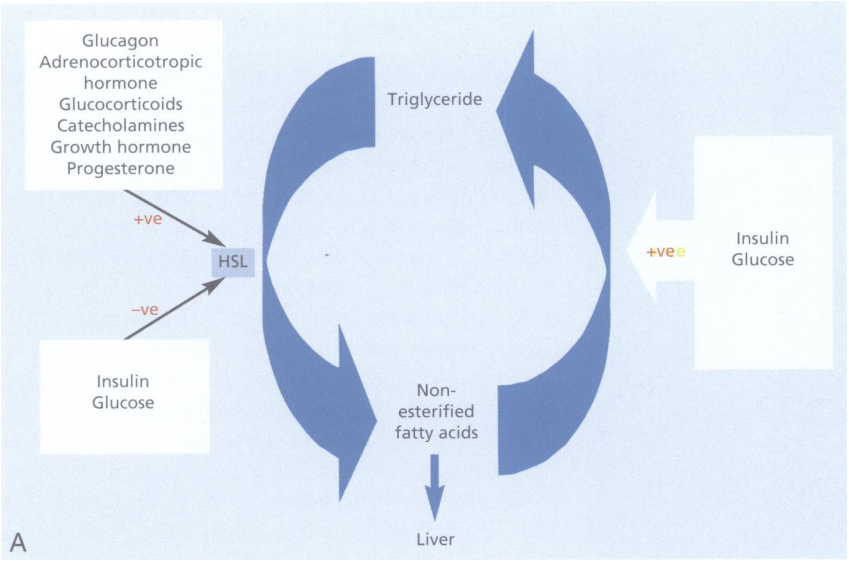
adipose tissue, and skeletal and cardiac muscle. LPL is inhibited by glucocorticoids, growth hormone and azotaemia, but its action is promoted by insulin and heparin.

Hyperlipaemia occurs when animals experience negative energy balance or stress, coupled with insulin resistance. The negative energy balance is a result of decreased dietary intake which leads to lipolysis as a normal response, but the insulin resistance leads to an unbalanced action of HSL (increasing fatty acid release and lipoprotein formation). Soon, fatty acid release overwhelms the liver's capacity for gluconeogenesis and ketogenesis and the fatty acids are esterified to form triglycerides. These are exported into the circulation in large quantities. The equine liver, in contrast to that of other large animal species, is efficient at synthesising and exporting triglycerides but is relatively inefficient at producing ketone bodies. The capacity of the skeletal and cardiac muscles to utilise these triglycerides is insufficient to prevent a build up of lipoproteins within the circulation. This is exacerbated by the reduced action of LPL in the face of insulin resistance. The resulting high levels of circulating triglyceride cause fatty infiltration of, primarily, the liver and kidneys. This can lead to organ failure if the process continues unchecked.

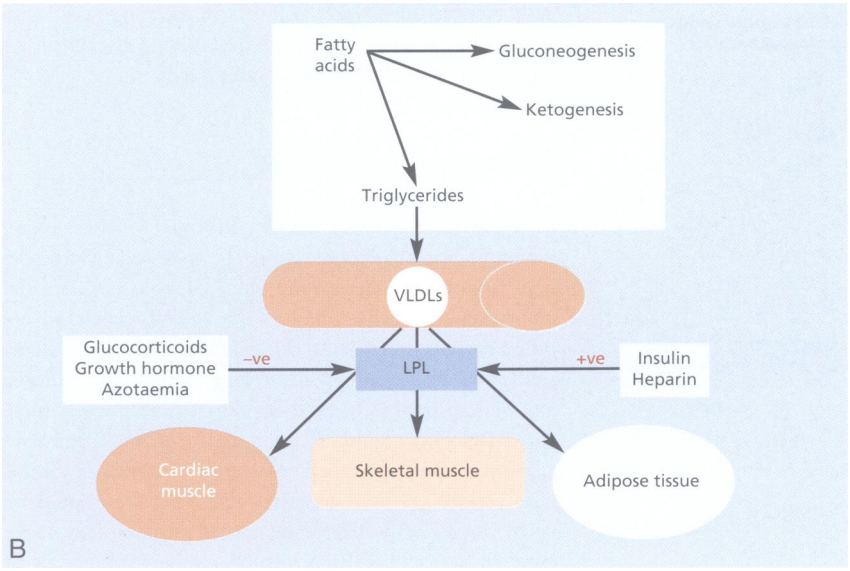
An understanding of these pathogenetic mechanisms helps to explain some of the risk factors. For example:

- Obesity provides large, readily available stores of fatty acids for immediate release and is also known to cause a degree of insulin resistance;
- Ponies and donkeys are relatively insensitive to insulin compared with horses;
- Pregnant mares experience insulin resistance up to 270 days of gestation due to one of the effects of progesterone (similar to the process that causes gestational diabetes in humans);
- Progesterone and growth hormone both promote HSL activity;
- Growth hormone antagonises LPL and may be partly responsible for pregnancy-associated insulin resistance;
- Animals with pars intermedia dysfunction and, consequently, increased circulating cortisol, show increased HSL activity and reduced LPL activity.

LPL is an enzyme active in the capillary endothelium. It acts to clear triglycerides (carried in VLDLs) from the circulation into adipocytes and skeletal and cardiac muscle. Thus, any decrease in its activity will increase the triglyceride levels in the circulation.



Pathogenetic mechanisms in equine hyperlipaemia. (A) Release of fatty acids from adipose tissue is under the control of hormone-sensitive lipase (HSL). As this enzyme's action is promoted by glucagon, and inhibited by insulin and glucose, it is more active during fasting. (B) In the liver, fatty acids are utilised to produce glucose or ketone bodies; any unused fatty acids are re-esterified to produce triglycerides. These triglycerides are exported in the circulation in very low density lipoproteins (VLDLs). The uptake of VLDLs by other tissues is under the control of the enzyme lipoprotein lipase (LPL). From Watson (1998)

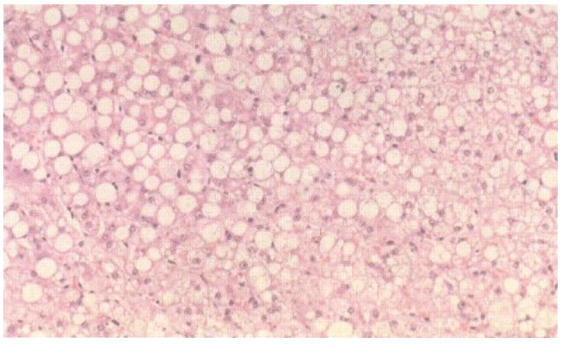


CLINICAL SIGNS

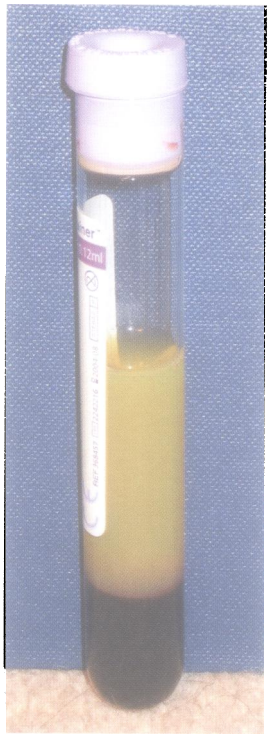
The most common presenting signs of equine hyperlipaemia are anorexia, depression and lethargy. Concurrent disease and secondary signs associated with liver or kidney failure may complicate the clinical picture.

Signs relating to liver failure include weight loss, icterus, skin lesions, diarrhoea, dysphagia, sham drinking, ataxia and head pressing. In the terminal stages, coma and convulsions are seen. There have been reports of sudden death relating to rupture of the liver due to gross swelling and it is assumed that, in the absence of primary gastrointestinal disease, colic symptoms are caused by stretching of the liver capsule.

Clinical signs relating to kidney failure include polyuria and polydipsia (although some cases may be confounded by pars intermedia dysfunction), tachycardia, congested mucous membranes and, occasionally, halitosis. Pregnant mares may abort, but this is often in the terminal stages. Some cases have marked ventral oedema, possibly as a result of subcutaneous fat thrombosis, liver disease causing portal hypertension or hypoalbuminaemia. Intestinal motility and faecal output are often reduced. Impactions are therefore common and a rectal examination should be performed where possible.



Photomicrograph of a section of liver stained with haematoxylin and eosin showing marked fat infiltration of the hepatocytes. Magnification x40. Picture, Dr B. Smyth



Blood sample showing opalescent serum

DIAGNOSIS

A diagnosis of hyperlipaemia should be considered in any fat pony or donkey that has recently become depressed and anorexic. The plasma of an affected animal will usually have a characteristic cloudy appearance due to the high concentration of circulating triglyceride. Interestingly, a recent study suggested that horses can be severely hyperlipaemic (with a triglyceride level of up to 18 mmol/litre) without there being any changes to the gross appearance of serum (Dunkel and McKenzie 2003). Thus, hyperlipaemia should be included in the list of differential diagnoses for any equid that is depressed and inappetent. A circulating triglyceride level of >5 mmol/litre is suggestive of hyperlipaemia while a level in the range of 1 to 5 mmol/litre implies hyperlipidaemia.

Despite the obvious appearance of the plasma, it is still worth obtaining actual values for the circulating triglyceride as these figures can be used to monitor the response to therapy. The prognosis does not appear to be directly related to the serum triglyceride concentration.

In severely affected animals, triglyceride levels can be as high as 65 mmol/litre. It should be noted, however, that some normal pregnant ponies and non-pregnant donkeys can have triglyceride levels in the range of 1 to 5 mmol/litre. Foals often have triglyceride levels of >1 mmol/litre due to suckling a high fat diet.

FURTHER ASSESSMENT

Serum biochemistry should be performed to assess organ function. Serum glucose should be assessed in order to help formulate a therapeutic plan. Glucose is often low on presentation, but may be increased secondary to pituitary pars intermedia dysfunction. Hydration status should be evaluated by measuring packed cell volume and plasma protein to help develop a fluid therapy plan. Renal function should be monitored by serum electrolyte analysis and measurement of serum activities of creatinine and blood urea nitrogen (BUN). Care should be taken when interpreting results as dehydration may cause prerenal azotaemia. BUN is not a reliable indicator of kidney dysfunction as it may be increased secondary to liver disease. If there is any doubt, urine specific gravity should be measured. In cases of prerenal azotaemia, urine specific gravity will be increased (>1·020), but will decrease following fluid therapy. Animals with renal failure will be isosthenuric (urine specific gravity 1·008 to 1·012).

Suggested biochemistry panel

- Triglyceride and glucose
- Hydration status
  - Packed cell volume
  - Plasma protein
- Renal function
  - Creatinine
  - Blood urea nitrogen
  - Electrolytes (Na^+, K^+, Cl^-, Ca^{2+})
- Blood gas analysis
  - Partial pressure of carbon dioxide
  - Partial pressure of bicarbonate
  - pH
- Liver damage
  - Sorbitol dehydrogenase
  - Gamma glutamyl transferase
  - Alkaline phosphatase
  - Aspartate aminotransferase
- Liver function
  - Bile acids
  - Ammonia

From Watson (1998)

Most cases of hyperlipaemia will present with compensated metabolic acidosis (ie, decreased arterial pH, partial pressure of carbon dioxide and bicarbonate, and an increased base deficit).

Liver disease should be evaluated by measuring gamma glutamyl transferase (GGT) as an indicator of biliary stasis or inflammation (although pancreatic disease is rarely recognised in the horse), sorbitol dehydrogenase (SDH) as an indicator of acute hepatocellular damage, and alkaline phosphatase (ALKP) and aspartate aminotransferase (AST), which are not liver specific. It should be noted that not all laboratories are able to perform SDH assays; however, if SDH measurement is possible, samples need to be presented to the laboratory quickly. Glutamate dehydrogenase (GLDH) measurement is a suitable alternative to SDH analysis. It is worth checking the laboratory's exact requirements before sending samples.

Measurement of bile acids can be undertaken to indicate liver dysfunction; increases over 15 µmol/litre are considered to be significant. Blood ammonia can also be measured, but samples need to be placed on ice and reach the testing laboratory quickly (in the author's experience, within the hour). Ammonia is associated with hepatic encephalopathy, although the degree of hyperammonaemia is poorly correlated with the severity of disease (some affected horses have normal levels of circulating ammonia). Bilirubin can also be measured, but the most common reason for hyperbilirubinaemia is anorexia which can make interpretation in such cases difficult.

Although necrotising pancreatitis has been reported in some animals with hyperlipaemia, measurement of serum amylase is usually unrewarding, with levels remaining within normal limits despite severe pathology. Pancreatic disease is thought to be caused by fatty vascular infarction or digestion of triglyceride by pancreatic lipase, followed by the release of cytotoxic fatty acids.

TREATMENT

Hyperlipidaemic animals should be considered 'at risk' of developing hyperlipaemia and care should be taken to ensure that a negative energy balance does not ensue. Additional stress should be kept to a minimum. The provision of a high energy feed either by voluntary intake or stomach tube is often enough to reduce triglyceride levels. In the hospital setting, this approach is adopted in some postsurgical colic cases, where treatment is aimed at correcting any azotaemia due to reduced enteral function by partial parenteral nutrition.

Concurrent disease should be assessed and treated on an individual basis. As a significant number of cases have parasitic burdens, anthelmintic treatment should be administered even where there is an apparently adequate worming history. Care should be taken to assess and, if possible, remedy any physical cause of dysphagia (eg, poor dentition). It has been suggested that ponies may

Goals of treatment

- Correct any underlying disease
- Correct negative energy balance
- Reduce circulating triglycerides
- Treat hepatic failure (if present)

benefit from treatment for pars intermedia dysfunction, if suspected. The author has treated cases with clear clinical signs such as hirsutism with concomitant polyuria and polydipsia. Diagnostic testing for pars intermedia dysfunction at this stage is not recommended as the resultant increased plasma corticosteroid levels will stimulate HSL and inhibit LPL.

Azotaemia, along with endotoxaemia, will inhibit LPL and must be corrected by supportive therapy. If renal function is adequate, intravenous fluid therapy with polyionic fluids containing lactate will be sufficient. This will also help to correct the metabolic acidosis. Care should be taken if additional bicarbonate is used to correct acidosis as it can exacerbate hepatic encephalopathy, cause respiratory depression and lead to alkalosis. Bicarbonate supplementation of intravenous fluids should only be carried out if there is access to blood gas analysis.

The energy demands of an affected animal should be reduced as much as possible (eg, lactating mares should have their foals weaned and animals which are outside in poor weather should be brought inside). Controversially, some authors advocate aborting mares, but this can potentially lead to retained fetal membranes which can result in metritis, laminitis and, hence, further stress. A selection of good quality palatable feeds should be offered, including freshly cut grass, sweet feed and sugar beet. A high energy gruel can be prepared using a complete pelleted horse feed mixed with water and passed via a nasogastric tube that can be left in place. Commercial equine enteral feeding solutions are available, but are expensive. Some horses have been managed successfully with human enteral solutions although, again, these are expensive. The author has had success with out-of-date human preparations obtained from a local hospital at no cost. A home-mixed diet, comprising electrolytes, water, dextrose, cottage cheese and alfalfa (Naylor and others 1984) can also be prepared. The daily energy requirements should be calculated and the total ration split into several feeds so that animals receive the correct amount of feed (see table on the left). The daily energy requirements are based on the formula for resting energy expenditure (REE):

DIVISION OF THE DAILY RATION

	Volume per feed
Miniature pony	2 litres
Large pony	5 litres
Horse (500 kg)	8 litres

$$REE\ (kcal/day) = 21 \times Bodyweight\ (kg) + 975$$

Box rest requires 1·2 x REE, while the 'stress-adjusted' figure is estimated to be between 1·2 and 2 x REE. A suggested protocol for enteral feeding – which involves building up the energy density over a number of days – is outlined in the box below. An alternative to this protocol is the administration of glucose by stomach tube. The recommended dose is 100 g of dextrose twice daily for a small (200 kg) pony. However, this can exacerbate the metabolic acidosis which is invariably present in these animals, and can potentially induce hypokalaemia. Hyperglycaemia can also exacerbate dehydration by creating an osmotic diuresis. For these reasons, galactose may be substituted for dextrose on alternate days as it is converted slowly to glucose, thereby reducing the risk of acidosis (see box above). The concurrent use of insulin is advocated in order to inhibit HSL and possibly reduce triglyceride release from adipose tissue. The dose of insulin is empirical as these ponies are generally significantly insulin resistant.

Suggested protocol for enteral feeding

- Day 1: 75 per cent REE
- Day 2: 100 per cent REE
- Day 3: 75 per cent stress-adjusted REE
- Day 4: 100 per cent stress-adjusted REE

Glucose administration: suggested regimen for a 200 kg pony

- Day 1: 100 g dextrose orally + 30 iu protamine zinc insulin intramuscularly, twice daily
- Day 2: 100 g galactose orally + 15 iu protamine zinc insulin intramuscularly, twice daily
- Day 3: Repeat day 1
- Day 4: Repeat day 2

If the gastrointestinal tract is compromised, parenteral nutrition should be administered. This is impractical outside the clinic setting due to the close monitoring required, and the risk of jugular thrombosis and sepsis. In the author's hospital, (non-lipid) partial parenteral nutrition (PPN) is administered using a 5:2 ratio of 50 per cent glucose and 8·5 per cent amino acid solution, with vitamin B supplementation in a balanced polyionic fluid, and additional electrolytes at a concentration based on the results of frequent electrolyte monitoring. The infusion is administered with a two-channel continuous infusion pump and is incrementally increased to achieve a minimum of 10 kcal/kg/day. This is ideally increased to 50 to 60 kcal/kg/day depending on economic constraints and patient tolerance.

The renal threshold of glucose in a horse is uncertain, but has been estimated to be in the region of 9 mmol/litre. Intravenous insulin infusion should be initiated where blood glucose levels approach these values. Alternatively, incremental amounts of insulin may be added to the PPN drip bag. The serum glucose is initially monitored every hour and adjustments made, if necessary. Even with this degree of monitoring it is possible to see major swings in plasma glucose levels. Parenteral nutrition is time consuming and expensive, but in the author's experience often results in normalisation of serum triglyceride within 24 hours; a quick resolution will reduce the overall cost of treating a particular case.

Some authors have recommended the use of heparin, at a dose of between 40 and 250 iu/kg, to reduce circulating triglycerides. Heparin promotes the action of LPL and, hence, clearance of triglyceride from the circulation. However, this is of questionable benefit as LPL activity is already increased by up to 300 per cent in hyperlipaemic ponies. In addition, heparin may increase the risk of coagulopathies (especially if there is concurrent liver failure), and unfractionated heparin may cause a marked reduction in packed cell volume. This reduction is minimised by using low molecular weight heparin. Heparin binds to LPL and releases it from its anchor points in the capillary endothelium. The heparin-LPL complex then attaches to VLDL and is directed to the liver, thereby increasing the burden on an already compromised organ. The author does not advocate the use of heparin for these reasons.

Nicotinic acid inhibits HSL and is used in humans and cattle. Its use has not been evaluated in horses. Other classes of drugs are used in hyperlipaemic humans, but are likely to be of limited benefit in the equine patient.

Treatment of liver disease in cases of hyperlipaemia is largely supportive. Hepatic encephalopathy is a poor prognostic sign, although one study reported that 40 per cent of patients with liver disease and hepatic encephalopathy were still alive after six months (this population was not, however, hyperlipaemic) (Durham and others 2003). Where hepatic encephalopathy is present, the main therapeutic option involves lowering circulating ammonia. Oral lactulose (0·3 ml/kg every six hours) acts to lower the intraluminal pH and, therefore, ammonia production and absorption. Oral neomycin (10 to 100 mg/kg every six hours) or oral metronidazole (15 mg/kg every eight hours) alters the gastrointestinal flora and decreases ammonia production. Prolonged treatment with neomycin should be avoided as it carries the risk of enteritis. Care should also be taken when using metronidazole as it can reduce appetite. Feeds with a high branched chain amino acid (BCAA) to aromatic amino acid (AAA) ratio (eg, sugar beet and maize) should be given, if possible, as AAAs are thought to be involved in hepatic encephalopathy. Commercial BCAA solutions are available, but are expensive. Vitamins B and K, and folic acid supplementation should be given weekly, as liver production of these will be compromised. A benzodiazepine receptor antagonist (Flumazenil; Roche) has shown potential in humans with hepatic encephalopathy, but may be prohibitively expensive for use in equine species.

PREVENTION

The prognosis in cases of equine hyperlipaemia remains poor. Prevention, through client education, remains the primary goal. Care should be taken with obese ponies and donkeys to ensure that a sudden negative energy balance does not occur (eg, in the management of laminitis). Studies have also shown that exercise improves insulin sensitivity within two weeks (Freestone and others 1992) and, hence, a controlled exercise programme, in combination with the administration of a diet that does not induce obesity, is recommended.

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