Equine Hyperlipidemias

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• Triglyceride • Energy • Metabolism • Nutrition • Hyperlipemia • Azotemia

Hyperlipidemias are defined by the presence of elevated lipid concentrations in the blood and are typically associated with periods of negative energy balance and physiologic stress. This increase in circulating lipids represents a normal physiologic response that serves to mobilize the energy reserves present in the fat depots of the body, but under certain circumstances, this response can become exaggerated and inappropriate. In increased concentrations, circulating lipids typically occur in the triglyceride form, and moderate increases in serum triglyceride concentration can lead to minor complications, with the most common being anorexia and depression. Increasing triglyceride concentrations can interfere with numerous normal physiologic functions, particularly in regard to reducing insulin sensitivity. This interference can result in the exacerbation of hyperlipidemia by impairing the ability of the body to limit fat mobilization, leading to worsening of lipid accumulation and severe complications, including renal and hepatic lipidosis and even death. Insulin-resistant individuals are at risk for hyperlipidemia, with the most commonly affected animals being ponies, miniature horses, and donkeys. The true incidence of hyperlipidemias in large-breed horses is not known, but these conditions seem to be increasingly encountered in the clinical setting, perhaps in relation to the increasing degree of obesity in the equine population.

DISORDERS OF EQUINE FAT METABOLISM

Dyslipidemias are disorders of lipid metabolism associated with abnormal amounts of circulating lipids. In horses, dyslipidemias present as hyperlipidemias, characterized by accumulation of circulating lipids in the form of triglycerides. Hyperlipidemias are most common in miniature horses, ponies, and donkeys but are uncommon in horses.[1] Several terms are used to describe equine dyslipidemias, including hyperlipemia, hyperlipidemia, hypertriglyceridemia, and severe hypertriglyceridemia

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(**Table 1**). Hypertriglyceridemia is present when serum triglyceride concentrations exceed the normal range (100 mg/dL) but is not associated with the evidence of clinical disease.[2] Hyperlipidemia is characterized by serum triglyceride concentrations from 100 to 500 mg/dL without gross lipemia.[3] Lipemia describes the presence of gross turbidity in a blood sample because of the presence of high concentrations of triglycerides but does not refer to a clinical syndrome (**Fig. 1**). Severe hypertriglyceridemia is defined as serum triglyceride concentrations exceeding 500 mg/dL, but in the absence of gross lipemia, which differentiates this condition from hyperlipemia.[3] Hyperlipemia is defined as a serum triglyceride concentration more than 500 mg/dL with visible lipemia and fatty infiltration of the liver or multiple organ systems.[2]

NORMAL ENERGY METABOLISM IN HORSES

Having evolved in sparse grassland environments, equine energy metabolism is based on the continuous intake of energy-poor diets, with roughage representing the primary feed source. Roughages contain variable amounts of nonstructural carbohydrates (sugars, starches), large quantities of structural carbohydrates (cellulose, lignin), and small amounts of protein and fat. Following ingestion, most of the nonstructural carbohydrates, proteins, and fats are absorbed in the small intestine. After absorption into the circulation, glucose can be used by tissues as an energy source or can be converted to either glycogen, for energy storage in the liver, or triglycerides, for energy storage in body fat. Insoluble carbohydrates, however, must undergo bacterial digestion in the hindgut to be absorbed in the form of volatile fatty acids (VFAs), and this process is shared by any soluble carbohydrates or proteins that reach the large intestine.[4] The primary VFAs are acetate, propionate, and butyrate. After absorption, these VFAs have different metabolic fates. Propionate is taken up by the liver and can be used for gluconeogenesis. Acetate and butyrate cannot be used for gluconeogenesis but can be used directly by some tissues as an energy source or are directed toward the synthesis of fatty acids, which occurs primarily in adipose tissue depots rather than in the liver.[5] Interestingly, because of their organization as hindgut

Table 1
Distinguishing characteristics of the various types of hyperlipidemias that have been described in horses

Equine Hyperlipidemias	Serum Triglyceride Concentration (mg/dL)	Gross Lipemia	Fatty Infiltration of Organs	Clinical Disease	Breeds Affected
Hypertriglyceridemia	>100	No	No	No	All
Hyperlipidemia	<500	No	No	No	All
Severe Hypertriglyceridemia	>500	No	Rare	Rare	Large-breed horses
Hyperlipemia	>500	Yes	Yes	Yes	Predisposed: ponies, miniature horses, donkeys Rare: large-breed horses

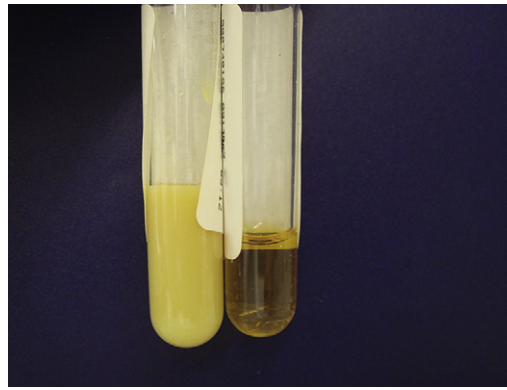

Fig. 1. Gross lipemia in a serum sample (*left*) as compared with a normal sample (*right*). (*Courtesy of* Dr Ramiro E. Toribio, College of Veterinary Medicine, The Ohio State University, Columbus, OH.)

fermenters, equids readily shift between the glucose-oriented metabolic pattern of the nonruminants when fed with diets high in soluble carbohydrates and a VFA-oriented metabolism similar to the ruminants when fed with a roughage-based diet.[6]

The normal metabolic response to intestinal glucose absorption is the release of insulin from the pancreas. Insulin clears glucose from the bloodstream and maintains serum blood glucose concentrations in a tight range (60–90 mg/dL). This function is achieved by increasing the tissue uptake of glucose, but if additional glucose is not currently needed as an energy source, it is converted into hepatic or muscle glycogen or depot fat. Insulin also suppresses the activity of hormone-sensitive lipase (HSL). HSL initiates the breakdown of triglycerides in adipose tissues, resulting in the release of glycerol, which is readily metabolized or converted to glucose, and free fatty acids (FFAs), which are metabolized via beta oxidation. HSL represents the rate-limiting step in the breakdown of fat, and if not regulated effectively, then excessive amounts of FFAs are released. FFAs not taken up by the peripheral tissues are normally removed from circulation by the liver and metabolized for energy, converted into ketone bodies, or esterified to form triglycerides. The liver processes the triglycerides into very-low-density lipoproteins (VLDLs) for export into the circulation. VLDLs are then transported to the peripheral tissues, where lipoprotein lipase (LPL) hydrolyzes the triglycerides from the VLDL, and the triglycerides are taken up by the cells of the peripheral tissues. LPL activity is stimulated by insulin and glucose-dependent insulinotropic polypeptide (GIP), which is a gastrointestinal hormone secreted in response to the ingestion of carbohydrates and fats.[7]

If a negative energy balance develops, several signals interact to maintain normoglycemia. First, the metabolic rate slows to decrease the consumption of glucose. Second, glucagon secretion increases and insulin secretion decreases, with the net effect being catabolic. Gluconeogenesis, glycogenolysis, and peripheral lipolysis ensue. In order to preserve the limited supply of glucose, there is a shift toward the use of fatty acids as a primary energy source. The release of leptin, a hormone expressed in adipose tissue, may increase as well, resulting in further energy release from fat stores. Because equids have limited stores of glycogen, maintenance of blood glucose concentrations is heavily dependent on gluconeogenesis, and protein catabolism increases to provide amino acids as precursors for glucose synthesis.

The response to a negative energy balance is increased in the presence of physiologic stress, such as that associated with illness or recovery from surgery. Increased endogenous glucocorticoid production is a normal response to physiologic stress, which leads to increased plasma cortisol concentrations and a loss of the normal circadian rhythm of cortisol production.[8] Cortisol inhibits insulin secretion and insulin actions but promotes catabolism and energy substrate mobilization. Increased catecholamine production in stress and illness upregulates the activity of HSL via stimulation of β-adrenoreceptors.[9]

DISTURBANCES OF ENERGY METABOLISM

Several factors can contribute to abnormalities of energy metabolism in equids, with the most common apparent cause being insulin resistance. Fasting has been shown to induce a state of insulin resistance in normal ponies,[10] whereas diets high in sugars and starches decrease insulin sensitivity in Thoroughbred weanlings and geldings.[11,12] Physical inactivity and increasing age also contribute to the development of insulin resistance.[13–15] Moreover, obese ponies and horses as well as ponies that have had laminitis are insulin resistant as compared with normal ponies or horses.[12,16,17] The association of obesity, insulin resistance, hyperinsulinemia, and hypertriglyceridemia with laminitis, particularly in ponies, has led to the characterization of the equine metabolic syndrome.[18,19] Pituitary pars intermedia dysfunction (PPID) has also been associated with hyperinsulinemia[13] and increased lipolysis in horses.[20] Complicating the management of clinically ill equine patients is the fact that systemic inflammation is associated with the development of insulin resistance, because several studies have shown that endotoxin administration induces an insulin-resistant state in horses.[21,22]

In animals with any or all of the aforementioned risk factors, the development of a negative energy balance can induce an inappropriate and excessive mobilization of peripheral fat stores. The liberated FFAs are converted into triglycerides within the liver, and the exported VLDLs accumulate within the circulation to excessive levels.[23] The increased circulating concentrations of FFAs and triglycerides can further complicate the normal homeostatic mechanisms that regulate energy metabolism, primarily by interfering with the actions of insulin. By preventing insulin from suppressing the activity of HSL, the rate of tissue lipolysis increases, worsening the hypertriglyceridemia. It has been shown that increased circulating FFA concentrations lead to the accumulation of lipid metabolites in muscle and hepatic tissue.[24] This accumulation disrupts the normal pathways that are responsible for insulin-induced glucose uptake in skeletal muscles and interferes with gluconeogenesis in the liver.[25] The result of all these interactions can be a fulminant self-perpetuating hyperlipidemia.

The accumulation of circulating lipids poses substantial risks to the patient, with the most severe being the possibility of tissue fat accumulation. The liver uses little FFAs for energy, and the pathway for ketone body formation is not well developed in horses, with the result that large amounts of triglycerides are produced. Excessive fat mobilization may overwhelm the capacity of the liver to process triglycerides into VLDL, leading to triglyceride accumulation and hepatic lipidosis. The kidneys are at risk of lipidosis as well, with renal lipidosis and/or azotemia reported in ponies and horses in association with hypertriglyceridemia.[3,26,27] The presence of azotemia may worsen hyperlipidemias by downregulating LPL activity.[28,29] Although the liver and kidneys seem to be at the greatest risk, there is evidence in other species that the pancreas may be damaged by fat accumulation as well, potentially contributing to the development of diabetes mellitus.[30]

DIAGNOSIS OF HYPERLIPIDEMIAS

The clinical signs of hyperlipidemias are nonspecific but most commonly include depression, anorexia, and decreased water intake.[3,31] More severe signs may include colic, fever, diarrhea, cachexia, and ventral edema.[2,26,31–34] Definitive diagnosis of hyperlipidemia requires documentation of increased levels of circulating lipids. Gross observation of a blood sample represents a simple means of ascertaining if lipemia is present (see **Fig. 1**), but lipemia is not present in all types of hyperlipidemias and is actually uncommon in large-breed horses affected with severe hypertriglyceridemia.[3] Serum triglyceride concentration should be measured as part of a routine serum biochemical evaluation in ponies, miniature horses, or donkeys because of their predisposition to hyperlipidemias and in hospitalized horses of all breeds because stress, illness, and hypophagia are common in the hospitalized population.

Hematologic changes are nonspecific and typically related to underlying disease processes but may include hemoconcentration, neutrophilia, neutropenia, left shift, and hyperfibrinogenemia.[3,35–37] Hyperlipemic ponies and donkeys are often hypoglycemic, although they are typically insulin resistant.[1] Metabolic acidosis is common in affected animals.[26,38] Azotemia is also frequent and may reflect either prerenal azotemia and/or renal dysfunction secondary to renal lipidosis.[3,26,34,39] Hepatic involvement may be demonstrated by increases in the serum bilirubin concentration as well as the hepatocellular and biliary enzyme levels.[3,26,31,34,35] Measurement of serum bile acid levels can be used to confirm the presence of hepatic dysfunction.

INCIDENCE OF HYPERLIPIDEMIAS

Hypertriglyceridemia, hyperlipemia, and hyperlipidemia are much more common in pony breeds, miniature horses, and donkeys, with Shetland ponies and donkeys being especially predisposed.[26,28,32] In one report, the incidence of hyperlipemia in ponies was 5.1 affected animals per 100 ponies per year.[33] Historically, the prognosis for affected ponies and donkeys has been reported to be grave, with mortality rates of 43% to 80%,[26,33,39,40] although recent reports showed mortality rates as low as 0% to 33% with aggressive treatment.[27,31,34,41]

Less is known regarding the frequency of hyperlipidemias in large-breed horses. Hypertriglyceridemia seems to occur more frequently in lactating or pregnant mares, and insulin resistance is reported to be more common in obese animals or in those with equine Cushing syndrome (ie, PPID) or the equine metabolic syndrome, but the actual rates of occurrence of hyperlipidemias in these groups are unknown. One retrospective study reported severe hypertriglyceridemia in 13 hospitalized horses in a 2-year period, which represented 0.57% of the hospitalized patient population.[3] The prevalence of obesity in large-breed horses seems to be increasing, particularly in pleasure riding horses that are fed high-grain diets but do not receive frequent high-intensity exercise.[42] This observation is supported by a recent publication from the United Kingdom, in which 45% of 319 pleasure riding horses were fat or very fat.[43] This trend toward increasing obesity is likely to contribute to insulin resistance and may result in an increased incidence of hyperlipidemias in large-breed horses, which argues for an increase in surveillance for hypertriglyceridemia in hospitalized horses.

PREVENTION OF HYPERLIPIDEMIAS

The most effective preventive approach is to avoid situations of stress and negative energy balance in animals likely to be susceptible to hyperlipidemias. Stressors can include transport, changes in management, and endoparasitism, all of which can be

avoided or controlled by appropriate management.[32,44] The avoidance of negative energy balance can be more difficult to achieve, especially in mares, because pregnancy and lactation represent unavoidable periods of negative energy balance. Similar challenges arise in attempting to prevent negative energy balance in hospitalized animals, particularly in those with gastrointestinal diseases that require enteral rest. In the clinical setting, early enteral feeding has been shown to be beneficial in humans and horses following intestinal surgery, and this approach is increasingly used in equine patients.[45] Since the first encounter of severe hypertriglyceridemia in the author's clinic, there has been an increased appreciation of the need for early nutritional support and the incidence of severe hypertriglyceridemia in hospitalized patients has decreased to near zero.

It may be possible to decrease the risk of hyperlipidemias in susceptible animals by taking measures to improve their insulin sensitivity. Because obesity is clearly linked with insulin resistance, there should be a benefit to normalizing the body weight of susceptible animals. Great care should be taken with this approach because dietary restriction is often the first step in reducing body weight. By definition, reductions of caloric intake induce a state of negative energy balance, however, and could induce the onset of the very hyperlipidemic conditions one is trying to avoid.[46] Careful application of dietary restriction can be effective in resolving obesity and restoring insulin sensitivity, as demonstrated by the study of Van Weyenberg and colleagues[47] in Shetland ponies. Although caloric restriction was effective, there was an increase in serum triglyceride concentrations throughout the study period, from a mean of 30 mg/dL to a mean of approximately 120 mg/dL.

Exercise may represent a more effective means of reducing body weight and adiposity. Even moderate increases in activity result in an increased metabolic rate and decreased adiposity, but short-term exercise is unlikely to improve insulin sensitivity for more than a few days.[14,48] One recent study concluded that exercise of higher intensity or longer duration induces greater decreases in body weight and adiposity and is likely necessary for improvement in insulin sensitivity in overweight or obese, insulin-resistant horses.[48] The optimal approach is likely to combine careful dietary restriction with an appropriate increase in physical activity, similar to what is prescribed in humans.

Feeding fat-enriched diets to both ponies and horses has been shown to increase the activity of LPL and improve tissue clearance of plasma triglycerides, likely by increasing the activity of GIP.[7,49] It has been suggested that feeding fat-enriched diets might be beneficial in animals susceptible to hyperlipidemias because of improvement in triglyceride clearance, but this approach should be considered with caution because of concurrent decreases in glucose tolerance and insulin sensitivity.[1,7]

The pharmacologic approach may improve insulin sensitivity in at-risk animals. Agents that have been reported to improve insulin sensitivity in horses include metformin and a synthetic thyroid hormone (levothyroxine). Metformin is an oral biguanide that is widely used in human medicine as an insulin-sensitizing agent, and it has been used in the management of insulin-resistant horses.[50] Metformin primarily controls blood glucose concentrations by inhibiting hepatic gluconeogenesis and glycogenolysis, but it also enhances peripheral tissue insulin sensitivity.[51] Although there is some evidence of efficacy in the literature, the drug is not well absorbed following oral administration in horses and is not recommended for use pending further information regarding pharmacodynamics in horses.[51]

The administration of levothyroxine sodium has been shown to induce weight loss and improve insulin sensitivity in horses.[19] This supplementation increases circulating thyroxine concentrations above the normal range, but signs of clinical hyperthyroidism

are not reported.[52] The current recommendation is that levothyroxine sodium should be administered to horses and large ponies at a dosage of 48 mg/d in the feed for 3 to 6 months along with modifications of diet and exercise, whereas smaller ponies and miniature horses should be given 24 mg of levothyroxine sodium daily.[19] Treated horses should be weaned from levothyroxine sodium therapy after the desired body weight is achieved, first by reducing the dosage to 24 mg/d for 2 weeks and then 12 mg/d for 2 weeks.[19]

MANAGEMENT OF HYPERLIPIDEMIAS

Effective management requires that clinicians identify the affected animals as early as possible to institute therapy before the hypertriglyceridemia becomes severe. The first line of surveillance is recognition of animals at risk by identifying the predisposing factors for hyperlipidemias. Gross observation of the blood for lipemia is not sensitive and should not be relied on in the clinical setting, and it is recommended that serum triglycerides be measured as part of the routine serum biochemical evaluation in clinically ill horses, and this evaluation is mandatory when evaluating any pony, miniature horse, or donkey.

Once hyperlipidemia is identified, the most important component of management is correction of the underlying condition that has resulted in a negative energy balance. Some conditions, such as pregnancy or lactation, are not easily addressed, but any primary disease process should be addressed as rapidly as possible. The second component of management is the correction of the patient's negative energy balance. If there is a lack of voluntary intake in a patient capable of tolerating enteral nutrition, then enteral supplementation is indicated. If the enteral route is unavailable, parenteral nutritional (PN) support is required.

Correction of Negative Energy Balance

The ultimate goal of dietary supplementation is the correction of the negative energy balance by meeting the patient's resting energy requirement (RER); however, there is some debate regarding the actual RER of the hospitalized equine patient. Hospitalized horses are stall-confined and inactive, thus consuming less energy than a horse at pasture or in routine work. In one study, the RER of stall-confined horses was 30% lower than that of horses at pasture.[53] More strikingly, the energy requirements of hospitalized premature foals or foals with hypoxic-ischemic encephalopathy were one-third of the energy requirement of healthy age-matched foals.[54] The determination of the RER is further complicated by the potential influence of physiologic stress or illness, which is demonstrated by the fact that anesthesia and experimental exploratory laparotomy in normal horses were associated with a 10% increase in resting caloric demand.[55] Given all these potential influences, a definitive RER value cannot be provided for all patients, but a reasonable RER value for most hospitalized mature equids is 22 to 23 kcal/kg/d.[56,57]

In reality, it can be challenging, particularly in the critically ill patient, to deliver the amount of energy required to meet the patient's estimated RER. Provision of excessive enteral nutrition may result in the development of diarrhea, which can be severe and even life threatening.[58] Provision of excessive PN can contribute to hyperglycemia, hypertriglyceridemia, or hyperlipemia, as well as electrolyte derangements.[57] For all these reasons, one should be conservative when initiating nutritional support, and a maximal target of 60% of RER is recommended.[41]

Indeed, in most cases it is not necessary to entirely correct the negative energy balance by meeting the patient's RER because the excessive lipid liberation is related

to the decrease in insulin secretion that accompanies decreased feed intake. This reduction in insulin secretion, particularly in horses conditioned to diets high in soluble carbohydrates, removes the normal suppressive effect of insulin on HSL. The increase in HSL activity leads to rapid liberation of large amounts of FFAs, and this response is exaggerated in the obese patient. To address this situation in the clinical setting, the solution may be as simple as providing small amounts of carbohydrates (5–10 kcal/kg/d) to stimulate endogenous insulin production. Despite providing less than one-fourth of the daily RER, this solution was effective in correcting hypertriglyceridemia in some large-breed horses.[3] Insulin resistance is likely to be present in any equid with hyperlipidemia, and in these patients, the administration of carbohydrates alone is likely to result in hyperglycemia. Insulin therapy is often required to overcome peripheral insulin resistance, allow for appropriate tissue uptake of glucose from the circulation, and restore normal HSL activity.

Enteral Nutritional Support

Provision of nutritional support by the enteral route is generally preferred because it is the most natural and physiologic means of nutrient delivery and the intestinal mucosa is partially dependent on the products of digestion for energy and nutrients. In addition, enteral nutrition is less expensive. If there is any question about the ability of the animal to tolerate feeding, then a thorough evaluation of the gastrointestinal function is needed before institution of enteral nutritional support. This evaluation should include abdominal auscultation, nasogastric intubation to evaluate for gastric reflux, and abdominal ultrasonographic examination. Horses with evidence of gastrointestinal dysfunction, such as gastric reflux, bowel distension, increased bowel wall thickness, or ileus, are unlikely to tolerate enteral feeding and should receive intravenous nutritional support. All efforts to encourage the voluntary intake of feed should be exhausted before instituting forced feeding.

A positive response may be observed with the oral administration of even small amounts (5 kcal/kg/d) of simple sugars. High-fructose corn syrup can be used as an oral carbohydrate source, but care must be taken not to feed excessive amounts to avoid carbohydrate overload. This product provides energy of approximately 4 kcal/mL, and horses typically accept it readily when administered orally using a dosage syringe. A 60-mL dose of corn syrup given orally every 2 hours delivers approximately 5 kcal/kg/d to a 500-kg horse and is well tolerated clinically. If more complete nutritional supplementation is required in the inappetant animal, the only alternative for the administration of enteral feedstuffs is the use of nasogastric intubation. Intermittent nasogastric intubation is often used for this purpose and can be effective. However, large-bolus feedings may overwhelm digestive capacity, and repeated intubation can be a stress for some patients. The primary advantage of intermittent intubation is that the large bore of the tube permits feeding slurry feeds, which more closely mimic the horse's normal diet. Use of small-bore indwelling nasogastric feeding tubes and feeding small volumes of liquid feedstuffs at frequent intervals (eg, every 1–2 hours) may be preferred over repeated passage of a nasogastric tube because the former decreases the risk of pharyngeal trauma and improves patient comfort. Another advantage of small-bore indwelling tubes is that they do not interfere with voluntary water or feed intake. Correct placement of small-bore feeding tubes should be confirmed by endoscopy because the flexible nature of these tubes makes it difficult to be certain of placement based on feel alone.

PN Support

Although the enteral route is generally preferred to provide nutritional support, there are a variety of situations in which a horse may be unable to receive enteral nutrition

or is unable to tolerate the required volume of enteral nutrition. In these circumstances, PN aids in delivering the appropriate caloric and nutritional support in a controlled manner and eliminates concerns regarding intestinal absorption and intestinal volume overload. The limitations of PN support primarily include the expense of this therapy and the risk of secondary complications. These complications may include hyperglycemia, hypertriglyceridemia, thrombophlebitis, and an increased risk of bloodstream infections.[59] Electrolyte abnormalities, such as hypokalemia, may develop with PN.

Short-term caloric supplementation

Carbohydrate solutions represent the simplest means of providing intravenous caloric support. After initial fluid resuscitation, electrolyte solutions containing added dextrose may be used as the primary fluids for maintenance therapy in horses with minimal ongoing fluid losses. The caloric content of a 5% dextrose solution is 0.17 kcal/mL, so an infusion rate of 5 mL/kg/h would be required to deliver approximately 20 kcal/kg/d. Unfortunately, this rate of infusion is up to 5 times that which is considered to be a maintenance rate for an adult horse (1–2 mL/kg/h), so a 5% dextrose solution cannot be depended on as a primary form of PN. However, electrolyte solutions containing 5% dextrose can be used to provide moderate amounts of carbohydrates to stimulate endogenous insulin production because an infusion rate of 1 mL/kg/h delivers 4 kcal/kg/d. Alternatively, a 50% dextrose solution can be delivered using an infusion pump, as long as additional isotonic fluids are being administered concurrently to avoid endothelial injury caused by the hypertonic nature of this solution. However, the use of a 50% dextrose solution should be avoided if an infusion pump is not available. The caloric content of a 50% dextrose solution is 1.7 kcal/mL, so an infusion rate of 0.5 mL/kg/h of this solution delivers approximately 20 kcal/kg/d. In patients that are likely to be incapable of enteral feeding for more than 24 hours, PN solutions containing carbohydrates and amino acids should be used rather than simple carbohydrate solutions. The provision of amino acids provides amino acid precursors for gluconeogenesis and limits endogenous protein catabolism. Lipid-containing PN solutions are typically only needed in patients likely to require prolonged parenteral support or those that are unable to tolerate carbohydrates. There is some concern that lipid-containing solutions could exacerbate preexisting hypertriglyceridemia, and for this reason, these solutions should be avoided in patients with very high serum triglyceride levels (>1000 mg/dL or gross lipemia).[57]

Insulin Therapy

The frequent presence of insulin resistance makes it difficult to achieve even a conservative rate of administration of intravenous nutrition in hyperlipidemic patients, and this difficulty can be addressed only by the administration of exogenous insulin. However, the administration of insulin to any patient requires diligent management to prevent profound hypoglycemia. Intermittent depot administration of subcutaneous insulin may offer some advantages in terms of simplicity of administration and moderation of effects, but this route of administration does not allow for changes in dosage over the short term. Subcutaneous administration may result in periods of hypoglycemia several hours after administration, but the simultaneous administration of oral carbohydrates can help ameliorate this effect. Close monitoring of blood glucose levels is required while determining the most appropriate doses of insulin and oral carbohydrates in each patient. In one report, 0.15 IU/kg of insulin zinc suspension was administered subcutaneously twice daily to ponies and donkeys, in conjunction with enteral or PN support, and the dosage of insulin was increased in increments of 0.05 IU/kg if hyperglycemia occurred.[41]

Insulin can also be administered as a continuous rate infusion (CRI), but patients receiving insulin should receive intravenous dextrose concomitantly to avoid hypoglycemia. The use of CRI insulin allows for a rapid onset of action while providing a timely means of adjustment of the dose. Because of the apparent gradual saturation of insulin receptors, the maximal effect of CRI insulin is not typically seen until approximately 90 minutes after initiation of therapy. The response to changing rates of infusion occurs over a similar time frame, so it is recommended to avoid altering the rate of infusion of PN solutions too rapidly after changing the rate of insulin infusion.

An initial insulin infusion rate of 0.07 IU/kg/h is generally well tolerated and represents a reasonable starting point for most patients. Simultaneous alterations should be avoided in both the insulin and the PN infusion rates because this can lead to a "roller-coaster ride," wherein the blood glucose concentration increases and decreases because of the delay in the body's response to these changes. Using a protocol in which changes in blood glucose concentration are primarily addressed by altering the insulin infusion rate can minimize dramatic alterations in blood glucose concentration.[60] Blood glucose monitoring should be performed at least hourly for the first 2 to 3 hours after initiation of the insulin CRI, and if hyperglycemia (blood glucose level >180 mg/dL) persists after the first 2 hours, the insulin infusion rate may be increased by 50%, followed by hourly blood glucose monitoring for a further 2 to 3 hours. This procedure may be repeated if hyperglycemia persists. Conversely, if hypoglycemia (blood glucose level <60 mg/dL) is noted, then a bolus of 0.25 mL/kg of 50% dextrose solution should be administered intravenously over 3 to 5 minutes. The blood glucose level should then be reassessed every 30 minutes for at least 90 minutes to ensure that hypoglycemia does not recur. If hypoglycemia does recur, then a second bolus of dextrose is administered, and the insulin infusion rate is decreased by 50%. Close monitoring is required for a further 60 to 90 minutes to ensure that hypoglycemia does not recur and hyperglycemia does not develop. Further changes to the insulin infusion rate are not usually necessary once a steady state has been achieved. Blood glucose monitoring should be done every 3 to 6 hours for the first day of therapy. The ongoing frequency of blood glucose monitoring depends on patient stability; blood glucose may not need to be monitored more frequently than every 12 hours in the stable patient. Patient reassessment is indicated if the patient has become even more insulin resistant (requiring additional insulin administration to avoid hyperglycemia), because this may be an early indicator of an overall deterioration in the patient's condition accompanied by increasing systemic inflammation. When PN is to be discontinued, it is recommended that the PN and insulin infusion rates be gradually reduced by 25% to 50% increments every 4 to 6 hours while gradually increasing enteral feeding. It is important that blood glucose monitoring is continued during this weaning process to prevent the development of severe hypoglycemia.

OTHER TREATMENTS FOR HYPERLIPIDEMIAS

Apart from correction of the primary disease and the provision of appropriate nutritional support, there does not seem to be any single specific therapy that is effective in resolving equine hyperlipidemias. The most widely discussed therapies include insulin and heparin administration. Inherently, insulin administration seems to be a logical therapy even in insulin-resistant individuals because it both suppresses HSL and activates LPL. The literature is conflicted, however, regarding insulin therapy as a primary treatment of hyperlipidemias in ponies, horses, and donkeys. Historically, the use of insulin was not associated with any apparent improvement in outcomes, and it was considered that insulin therapy might be ineffective because

excessive fat mobilization was secondary to insulin resistance.[31] Alternatively, it seems possible that there was an inherent selection bias, wherein the animals most likely to receive insulin therapy were those with profound insulin resistance and refractory hyperglycemia, and these individuals seemed to have more severe hyperlipidemia and were less likely to survive. Recent studies have reported that insulin, when administered concurrently with appropriate nutritional support, seems to aid in the resolution of hypertriglyceridemia.[27,41]

Heparin has been used in the treatment of hyperlipidemias because it promotes peripheral triglyceride use and stimulates LPL activity.[31,32,39,61] The efficacy of this treatment has been questioned because the activity of LPL was not deficient in hyperlipemic ponies but was, in fact, increased 2-fold.[23] Heparin therapy has also been questioned because of the risk of heparin-induced thrombocytopenia and bleeding disorders.[31,62] On the other hand, heparin has been shown to be effective in both equine and human patients in rapidly reducing plasma triglyceride concentrations and may be useful in managing the severely hypertriglyceridemic (>1000 mg/dL) or lipemic patient.[41,62] If used, treatment with heparin should be for a very short term to minimize the risk of side effects.

SUMMARY

Although the risk of hyperlipidemias is greatest in ponies, miniature horses, and donkeys, all equids are potentially at risk if they are in a situation involving a negative energy balance. The sedentary lifestyle of many modern horses and the frequent feeding of high-carbohydrate diets mean that increasing numbers of animals are at risk of obesity and insulin resistance. Both these factors contribute substantially to the risk of excessive fat mobilization and the development of hyperlipidemias. Veterinarians can decrease the risk to their patients by being vigilant for those individuals most likely to be insulin resistant and instituting appropriate monitoring, prevention, and management strategies.

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