

## **Hepatic Lipidosis in Cats**

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## Hepatic Lipidosis

Hepatic lipidosis is the most frequent cause for severe liver failure in cats seen at the University of Minnesota Veterinary Teaching Hospital and is also the most common primary hepatobiliary disease seen in cats at the Animal Medical Center in New York. Although lipidosis occurs in dogs, it is a relatively mild phenomenon, and not often associated with clinical signs. The normal liver contains approximately 5 per cent lipid which may exist as triglycerides, fatty acids, phospholipids, cholesterol, and cholesterol esters. However, when significant fat accumulates in the liver it is nearly always triglyceride and may be 40 to 50 per cent of the total liver weight. Normal hepatic lipid arises from multiple sources, the most important are the diet, from mobilization of fatty acids out of peripheral fat stores, and from endogenous fatty acid synthesis in the liver. Circulating fatty acids are carried in the bloodstream bound to albumin. Upon reaching the liver they are removed and incorporated into triglycerides, if they are not oxidized for energy. Triglycerides are complexed with specific proteins (apoproteins) forming lipoprotein particles (very low density lipoprotein, VLDL), which are secreted back into the circulation. If the rate at which fatty acids are brought to the liver exceeds the liver's ability to metabolize or resecret them back into the circulation as VLDL, storage of fatty acids as triglycerides (lipidosis), occurs. The normal liver is capable of extracting fatty acids from blood at rates that exceed the liver's capacity either for synthesis or secretion of VLDL. Thus, excess triglyceride accumulation in the liver is easily accomplished

### Etiopathogenesis of lipidosis

Processes which lead to lipidosis are associated with one or more of the following: there is increased delivery of fatty acids to the liver, either from the diet or in association with peripheral lipolysis; there is decreased hepatic fatty acid oxidation; or there is decreased ability to secrete VLDL back into the circulation.. In the process of VLDL formation, adequate dietary intermediates such as choline, methionine, cysteine, betaine, or casein are necessary for phospholipid formation. Thus, fatty livers that respond to lipotropic agents such as choline are physiologic fatty livers and are due to dietary deficiencies of these compounds. In most clinical diseases associated with lipidosis, deficiencies of these substances do not exist, and supplementation with lipotropic agents, especially methionine, does no good, and may be harmful (see therapy section).

The most important causes for lipidosis in dogs and cats are starvation, diabetes mellitus, obesity, drug injury, and toxicities. Of these, the severe lipidosis seen in obese cats associated with prolonged anorexia is the most clinically significant, and may account for as much as 62 per cent of all cases. Although lipidosis may develop in cats in association with any of the above mentioned mechanisms, in the overwhelming majority of cases with severe, clinically apparent liver failure, the cause, other than the association with starvation, is unknown. This syndrome has been called idiopathic feline lipidosis to distinguish it from cases induced by other recognizable causes, such as diabetes mellitus, drugs, and so forth. Starvation in other species is generally associated with mild degrees of fatty liver and subtle clinical disease. In cats however, severe idiopathic lipidosis often has a fatal outcome. Why anorexia is associated with such a severe disease in cats is

currently unknown. In starvation, a lack of availability of dietary glucose causes increases in growth hormone secretion and sympathetic activity, and decreased insulin release. These processes lead to accelerated peripheral lipolysis and massive free fatty acid release into the circulation. Fatty acids are taken up by the liver and converted to triglycerides. In states of protein-calorie malnutrition, it appears that accumulated triglycerides are not efficiently converted to VLDL due to failure of lipoprotein synthesis and secretion.

Several hypotheses have been proposed as to why some cats, particularly obese cats, develop such severe lipidosis in association with anorexia. Cats of normal size are apparently able to tolerate long periods of starvation without developing this severe complication. A relative deficiency of arginine may be important as a cause for idiopathic feline lipidosis. Arginine is an essential amino acid for cats, and during periods of starvation, it is supplied by muscle catabolism. Arginine is an important intermediate in the urea cycle and deficiencies lead to rapid development of hyperammonemia and encephalopathy in cats. If a relative deficiency of this amino acid exists, it would lead to encephalopathy which would lead to anorexia and perpetuate the disease.

A deficiency of arginine can also result in reduced quantities of ornithine, another intermediate in the urea cycle. Lack of sufficient ornithine causes concentrations of carbamoyl phosphate to increase within hepatocytes. Carbamoyl phosphate is metabolized to orotic acid. Orotic acid is known to induce severe lipidosis by interfering with lipoprotein secretion from the liver which can be reversed by adenine. Cats require a minimum of 1.1 per cent of arginine in the diet, and when arginine is deficient, urinary orotic acid concentrations increase proportionately. Serum concentrations of orotic acid and arginine have not been evaluated in these cats.

Carnitine deficiency has also been proposed as a possible mechanism for idiopathic feline lipidosis. This is based on information from humans in which rare cases of severe lipidosis are due to a deficiency of carnitine. Carnitine is necessary for oxidation of hepatic triglycerides, and in its absence, patients develop severe lipidosis, hepatomegaly, and hypoglycemia. Concentrations of carnitine are decreased in plasma, muscle and liver tissue. The feline disease bears minimal similarities to the human syndrome.

Endocrine abnormalities, particularly a relative or absolute insulin deficiency has been proposed to play a role in feline lipidosis. A few of these cats have had impaired glucose tolerance and mild intermittent hyperglycemia. These cats are often obese, and obesity can cause insulin resistance. Insulin resistance or decreased insulin secretion results in accelerated lipolysis and increased circulating fatty acids. The role that subclinical diabetes may play in this disease is unknown. A recent study of 150 cats found that fasting blood glucose values were higher in cats with mild to moderate lipidosis than in those with the most severe disease.

### Clinical Features of Lipidosis

Cats with lipidosis have no age, sex or breed predispositions, although most cases are over 2 years of age. Nearly all cats have been partially or completely anorectic for some period of time (median 2 to 3 weeks). The more complete the anorexia and the

longer the duration, the more severe is the disease. The cause for anorexia may be associated with some stress in the cats life such as moving, kenneling, addition of new pets, or a minor clinical disease. Some cases are caused by attempts to change the cats diet. Cats that have marked dietary preferences will starve rather than eat a new type of food, and may develop severe lipidosis. Many cats were obese prior to the onset of the disease and have had significant weight loss, up to 50 per cent of their body weight. Cats are typically depressed, and lethargic, may vomit occasionally, hypersalivate and show other signs of hepatic encephalopathy. Upon physical examination, these cats are usually thin, have pronounced muscle wasting but still maintain intraabdominal fat stores. Hepatomegaly is considered uncommon by some but has been frequent in cases evaluated by the author. Jaundice is present in most animals.

Laboratory evaluations on these cats identify the severity of the hepatic failure present. Mild to moderate, non-regenerative anemias and mild neutrophilia are present in a few cases. Biochemical profiles usually indicate marked increases in serum concentrations of AP, ALT, and AST. Bilirubin, gamma glutamyltransferase (GGT), and serum bile acid concentrations are also mildly to markedly increased. In contrast to most other feline liver diseases, AP concentrations frequently are 2 to 4 times the magnitude of rise of GGT. Blood glucose, serum cholesterol, and triglyceride concentrations are infrequently increased, and hypoalbuminemia is uncommon. Blood ammonia concentrations may be increased. The most consistent abnormality in the urinalysis is the presence of bilirubin. A definitive diagnosis requires biopsy. This is a diffuse disease, and percutaneous needle biopsies are an efficient, rapid method of obtaining a diagnosis. In fact, the diagnosis can sometimes be made from cytologic evaluations of fine needle aspirations alone. An estimate of clotting status is important prior to obtaining a liver biopsy in these cats. Mild to marked coagulopathies are sometimes present. Fresh whole blood should be given to cats with coagulopathies prior to attempting a liver biopsy. Grossly, these livers are swollen, yellow and friable. They have a prominent reticulated pattern to their surface. The biopsy will float when placed in formalin. A rapid tentative diagnosis can be made cytologically from a touch imprint of the specimen. Hepatocytes are diffusely swollen with numerous pale staining large fat droplets that displace the majority of the cytoplasm to the periphery of the cell.

Two forms of vacuolation may be observed histologically, macrovesicular and microvesicular. The macrovesicular form is characterized by one to several very large vacuoles within the hepatocyte that displace the nucleus and cytoplasm to the periphery of the cell. The microvesicular pattern has multiple small fat vacuoles distributed throughout the hepatocyte cytoplasm and the nucleus is centrally located. In humans, the macrovesicular pattern is most often seen with alcoholism, starvation and malnutrition, while the microvesicular pattern is typical of Reye's syndrome and acute fatty liver of pregnancy associated with tetracycline use. Although this difference has been thought to represent a different pathogenesis, it more likely reflects a difference in the severity and duration of fat accumulation. With chronic, progressive lipidosis there is aggregation of smaller triglyceride droplets into large aggregates. For fat to be definitively identified on tissue sections, specimens must be stained with oil red-O on fresh frozen samples or formalinized tissue. Fat is normally lost in the processing of most tissue sections. Inflammatory reactions are usually minimal in these biopsies. Prominent cholestasis will be seen in many specimens and be evident as bile plugged canaliculi.

## Therapy of Feline Hepatic Lipidosis

The therapy of lipidosis should be directed at the cause, if known, combined with aggressive supportive and symptomatic care. Most published reports of idiopathic feline lipidosis indicate the disease is nearly always uniformly fatal. Until the past two to three years this has been the author's experience as well. However, once we began utilizing aggressive nutritional support in these cats our success rate has improved dramatically. We have increased the survival rate from 5 to 10 per cent to 50 to 60 per cent survival now. The only significant change has been more aggressive oral alimentation and persistence. In addition to standard supportive and symptomatic therapy for animals in hepatic failure (fluids, oral neomycin and/or lactulose, vitamin supplementation), we combine force feeding of a reduced protein diet (feline k/d) either as meat balls or a gruel if the animal will tolerate that method. If we have to fight the cat to force feed it, or it is too depressed for that method to be effective, we feed them with a 3 or 5 French diameter soft rubber nasoesophageal catheter. The distal end of the catheter is sutured to the cat's forehead and an Elizabethan collar is put on the cat to keep it from removing the catheter. Commercial canned cat foods cannot be blenderized sufficiently to get them to pass through these small catheters. A nutritionally complete liquid diet for use in humans (Ensure-HN, or Impact) has worked well as nutritional support in many of these cats. This diet must be mixed 50:50 with water to get it to flow easily through the catheter. The catheter must be flushed with water after each feeding to keep it from plugging. We attempt to administer the total daily caloric requirements for these cats by this means. The cat will have to be fed small quantities multiple times per day. If large volumes are administered, vomiting often results. Diarrhea may develop due to the high fat content of these liquid diets. We start with 2 to 3 ml/lb/feeding initially and gradually increase this volume until 2.5 to 3.5 ml/kg can be given at one time. Some cats will not tolerate intermittent boluses, and we have used a continuous feeding pump to slowly infuse the required food throughout the day. Not only can the caloric requirements of the cat be met this way, but fluids, electrolytes, lactulose and neomycin can also be given by this route. Although pharyngostomy tubes allow for larger diameter feeding tubes to be used, they require general anesthesia for placement and are not well tolerated by many cats for long-term use. Endoscopically placed tube gastrostomy is an alternative to nasoesophageal catheters, and is an efficient way to administer normal volumes of commercial low protein diets to cats for long term maintenance of anorectic cats. Many cats can be sent home with the tube in place, allowing owners to provide the nursing care necessary to salvage these animals once the patient is stabilized in the hospital. We also use benzodiazepines to stimulate appetite in cats that are still willing to voluntarily consume food. They will be covered in the therapy section to follow.

Recovery in these near terminal cats is not a rapid process. We have maintained several cats on forced alimentation for 8 weeks or more, until they began to show an interest in eating. Such cats will look unhealthy for quite some time before they start to make any obvious clinical improvement. Once they start eating on their own, the prognosis is good. The author firmly believes many more cats can be saved with persistent effort. Several survivors looked like they were not going to turn around after 3 or 4 weeks of effort, but through perseverance, these cats are now totally normal. They

serve as a reminder not to quit too early in the treatment of this disease. Biochemical recovery is also slow to become evident. A number of these animals have been back to eating on their own yet chemistry profiles were not significantly different from those obtained at the height of their illness. Idiopathic feline lipidosis is potentially completely reversible.

Diabetes is the only other major cause for lipidosis that occurs with any frequency in dogs and cats. In dogs, the disease is primarily a biochemical problem; rarely is it associated with clinical illness. This is generally true in diabetic cats as well. However, some diabetic cats with severe lipidosis do not reverse rapidly once the diabetes is regulated and will need to be managed as described above for the idiopathic disease. In diabetic dogs, serum ALT concentrations are increased mildly in approximately 50 per cent of cases. In contrast, serum AP concentrations are nearly always increased. The magnitude of rise is variable, but three-to five-fold increases are common. Retention of BSP may be in the 6 to 12 per cent range. Hyperbilirubinemia is uncommon, and when present, is mild.

Toxic injury is another potentially important cause for lipidosis. Many toxins can induce hepatic lipidosis if they interfere with hepatic protein synthesis. Bacterial endotoxins absorbed from the gut are well established causes for mild lipidosis. Treatment with oral antibiotics significantly reduces the severity of these lesions by suppressing colonic bacterial toxin production.

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