Nutritional Considerations for Dogs and Cats with Liver Disease

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ABSTRACT

The goals of nutritional management of liver disease in the dog and cat are directed at treating the clinical manifestations as opposed to treating the underlying cause. Specifically, the clinician strives to avoid overwhelming the remaining metabolic capacities of the damaged liver while providing sufficient nutrients for regeneration. A brief overview of liver diseases and associated clinical signs encountered in the dog and cat and a review of specific nutrients are discussed as well as amounts and sources of nutrients recommended to meet nutritional goals in the diseased liver.
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Introduction

Common liver diseases in companion animals include acute or chronic hepatitis, cholangitis, vascular anomalies, toxicosis, hepatic lipidosis, and neoplasia. The liver provides many essential functions, including synthesis and metabolism of carbohydrates, fats, and proteins. Therefore, liver disease can potentially affect metabolism and utilization of all macro- and micronutrients. Treatment of liver disease requires a multimodal approach, which can include medications, surgery, supplements, and dietary modification. Goals of nutritional management are centered on the avoidance of overwhelming the remaining metabolic capacities of the damaged liver and prevention of clinical signs such as hepatic encephalopathy (HE) while providing sufficient nutrients for regeneration. The aim of this paper is to discuss the various nutrients that are involved in dietary management of patients with liver disease.

Common Clinical Signs and Medical Treatment of Patients with Liver Disease

Liver disease can vary widely from simple elevations in liver enzymes (alkaline phosphatase and alanine aminotransferase) without clinical signs to severe cirrhosis with HE, ascites, and other life-threatening manifestations. Both medical management and nutritional therapy are based more on clinical signs and specific causes than liver enzyme elevations. Clinical signs of liver disease vary widely with the nature and severity of disease. Common early signs include lethargy, vomiting, diarrhea, and hyporexia. Jaundice, polyuria, and polydipsia can be found at any stage, depending on the etiology of the liver disease. Hypoglycemia, petechiae, ecchymoses, melena, and hematochezia can be seen in advanced liver disease with decreased functional liver mass, such as in cases of severe fibrosis and cirrhosis, or in cases of portal hypertension. Portal hypertension and/or hypoalbuminemia can lead to formation of ascites. HE is a consequence of advanced liver disease that results in a variety of signs including altered mentation,

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AAA, aromatic amino acids; AAFCO, Association of American Feed Control Officials; BCAA, branched chain amino acids; BCS, body condition score; DER, daily energy requirements; DM, dry matter basis; IBW, ideal body weight; HE, hepatic encephalopathy; NRC, National Research Council; RER, resting energy requirements

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incoordination, tremors, and seizures. Cats commonly develop ptyalism in addition to the aforementioned signs.

Treatment of liver disease depends on both the underlying cause and the clinical signs, and the reader is directed to other sources for a more comprehensive discussion of the specific treatments available.[1,2]

Energy

Energy requirements may be increased from normal estimated daily energy requirements (DER) because of the catabolic nature of liver disease. However, patients with liver disease frequently have a decreased activity level, which may complicate calculations of energy requirements. Patients may fall below or above standard calculations for DER (1.4–1.8 x resting energy requirements [RER] for dogs and 1.0–1.4 x RER for cats; RER = 70 x (body weight kg)$^{0.75}$). DER factors depend on activity level, energy expenditure, and sexual (spay/neuter) status. In addition, it is recommended to calculate ideal body weight (IBW) for dogs and cats that are underweight or overweight and use the IBW to calculate RER and DER. IBW can be calculated using one of many formulas, which are better described for overweight patients but can be used for underweight patients as well.[3]

Many patients with liver disease are underweight with acute or chronic hyporexia and require an energy-dense diet to minimize the volume of food necessary to meet DER. Diets with increased fat and decreased fiber content can increase palatability for patients with hyporexia and increase the energy density of the diet, making it easier to meet DER and maintain body weight and body condition score (BCS). A higher-fat diet can also be more beneficial for patients with prolonged anorexia because of the metabolic shifts that occur during starvation. After prolonged anorexia or severe hyporexia, patients shift to utilization of fatty acids and ketone bodies for energy, and less glucose is used for energy.[4] In addition to providing an energy-dense diet, tactics such as warming the patient's food or hand feeding may be beneficial to improve palatability and appetite, and appetite stimulants such as mirtazapine or cyproheptadine may be necessary. Mirtazapine induces minimal inhibition of the cytochrome P450 enzymes.[5] Recent studies have shown that in healthy cats, daily dosing of mirtazapine is safe and results in an increased appetite. While every-other-day dosing at 1.88 mg/cat is recommended for cats with chronic kidney disease, the safest dose schedule is not known for cats with hepatic disease, although renal and hepatic clearance is similar for mirtazapine. Idiosyncratic hepatotoxicity (elevation in alanine transaminase) has been observed in one healthy cat, so it is recommended to monitor liver enzymes while the patient is receiving mirtazapine.[6–8] Cyproheptadine is metabolized in the liver and excreted in the urine, and there are no reports of dosage reductions for patients with liver disease.[5]

For patients that are overweight, it is usually more appropriate to treat the primary disease prior to implementing a plan to achieve IBW and ideal body condition, especially if they are critically ill.[9] Food intake can be monitored by measuring body weight and monitoring BCS, and the recommended intake (DER) can be adjusted to meet the individual patient's goals. Anorectic or hyporexic patients often benefit from placement of feeding tubes (gastrostomy or esophagostomy) to assist in achieving adequate nutrition. If feeding tubes are utilized, it is recommended to start feedings at 1/4–1/3 RER and gradually increase the amount fed to achieve DER over the span of 4–7 days.

Soluble/Digestible Carbohydrates

The liver plays a major role in the metabolism of monosaccharides and is the primary site of gluconeogenesis. Glucose that is produced in the body as well as glucose that is provided by the diet is stored in the liver and muscles as glycogen, used for synthesis of fatty acids, and oxidized for the production of energy via glycolysis, which is the breakdown of glycogen to glucose and ATP via anaerobic metabolism.[10,11] As a result of the liver's involvement in carbohydrate metabolism, liver dysfunction can lead to derangements in glucose metabolism that may result in hypoglycemia or hyperglycemia. Recommendations for dietary soluble carbohydrates can be higher than those recommended for healthy patients to ensure adequate glucose intake, especially in patients with cirrhosis, congenital portovascular anomalies, hepatic failure, and extensive hepatic neoplasia.[10,12] Increasing intake of dietary soluble carbohydrates relative to current intake is beneficial in dogs and cats that have difficulty maintaining blood glucose levels and tend to be hypoglycemic. Soluble carbohydrates, when increased for patients with the tendency to be hypoglycemic, should include highly digestible carbohydrates such as white rice. Complex carbohydrates, including whole grains, should be avoided in these patients.

Dietary soluble carbohydrates can be problematic in some patients and should be limited in certain conditions, such as hepatic lipidosis to prevent diarrhea, abdominal pain, and hyperglycemia.[12] Hyperglycemia can also occur in patients with prolonged anorexia who receive nutritional therapy too quickly, such as those who receive nutritional support via a feeding tube or parenteral nutrition. Refeeding syndrome can occur in extreme cases from changes in insulin levels, resulting in derangements in glucose, potassium, phosphorus, and magnesium.[13] While patients are hospitalized, parenteral supplementation of these nutrients may be necessary. As a result, patients with prolonged anorexia should

not receive high levels of dietary carbohydrates. As mentioned previously, prolonged anorexia or even prolonged hyporexia can result in metabolic shifts, making it more difficult for the body to utilize carbohydrates.[4] Serum electrolyte, glucose, phosphorous, and magnesium levels should be monitored closely in the first 4–7 days of refeeding to determine if nutrient adjustments are necessary. Daily or more frequent monitoring of glucose, potassium, phosphorus, and magnesium is recommended until the patient reaches full RER and appears stable.

Carbohydrates are not recognized as a required nutrient by the National Resource Council (NRC) or by the Association of American Feed Control Officials (AAFCO); therefore, there is no minimum or maximum requirement published for dogs or cats.[14,15] For that reason, specific goals for providing dietary carbohydrates should be determined on an individual patient basis. One source indicates that for patients with liver disease, no more than 45% of total calories (metabolizable energy) should come from soluble carbohydrates.[16] However, this number may need to be exceeded for protein- and/or fat-restricted diets, as dietary carbohydrates must increase to provide sufficient calories if calories from protein or fat are decreased. If a patient is hypoglycemic or hyperglycemic, the best recommendation is to increase or decrease soluble carbohydrates relative to current intake, respectively. For hyperglycemic patients, providing fewer calories from carbohydrates and providing calories from complex carbohydrates may help decrease hyperglycemic tendencies.

Dietary Fiber

Total dietary fiber, which is reported on the labels of human foods, is a combination of insoluble fiber and soluble fiber. Crude fiber is listed in the guaranteed analysis of all pet foods and only represents insoluble fiber. Soluble fiber is not a component of crude fiber, and the reported crude fiber is not representative of the total dietary fiber or soluble fiber content in a food.[17] Insoluble fibers such as cellulose are nonfermentable, while soluble fibers, including pectins, plant gums, and some oligosaccharides, can be fermented in the gastrointestinal tract.[15]

Feeding diets high in soluble fiber or adding soluble fiber such as psyllium husk to existing diets may have some benefit in dogs and cats with liver disease. Soluble fiber, because it is fermentable, can alter the bacterial flora, reduce enteric ammonia production, and increase both fermentation of lactulose and fecal bile acid excretion. Soluble fiber also traps ammonia in the colon to enhance fecal nitrogen elimination. The effects of soluble fiber may mimic effects of lactulose and reduce clinical signs of HE.[12] Potential adverse effects of adding fiber to a diet can include reduced nutrient absorption and digestion, poor palatability, and decreased energy density.[12] Psyllium husk can be dosed in convenient amounts for the patient's owner, basing the dose on the patient's body weight and having clients measure it in units of 1/8 teaspoon per 10 lb twice daily depending on the fiber content of the current diet and patient tolerance. There is no published dose for soluble fiber administration specifically for patients with HE.

Dietary Fat

The liver is a source of synthesis and transport of lipids from digestion and absorption via synthesis of bile salts and secretion of bile. Fatty acids, triglycerides, phospholipids, cholesterol, ketones, and bile salts are all synthesized in the liver, and the liver is also the source of lipoprotein metabolism. Hepatic dysfunction can lead to imbalances in the uptake, synthesis, utilization, and release of fatty acids. In some patients with liver disease, poor bile salt secretion contributes to malabsorption of cholesterol, long-chain fatty acids, and fat soluble vitamins (A, D, E, and K) because of the absence of micelle formation.[11] For example, patients with severe cholestatic disease may develop steatorrhea because of reduced bile secretion inhibiting fat absorption.[11]

Recommendations for dietary fat for patients with liver disease can be increased or decreased compared to healthy pets. In general, the goal is to meet DER and maintain the patient's optimal body weight. A diet with an increased fat content can increase palatability for patients with reduced appetites while increasing the calorie density, thus making it easier to meet energy requirements. In addition, because fat is the most energy-dense nutrient, dietary fat can be beneficial for underweight patients. However, it is contraindicated to utilize high-fat diets (>40 g/1000 kcal for dogs or > 60 g/1000 kcal for cats) in dogs with a history of pancreatitis, in dog breeds predisposed to pancreatitis, in cats or dogs with hyperlipidemia, in overweight cats or dogs (BCS > 5/9), and in cats or dogs with severe cholestatic disease. The appropriate amount of fat for dogs and cats with various diseases is largely unknown, and there is variation among clinicians.

Protein

Protein should not be restricted unless signs of HE are present. Protein requirements set by the NRC and AAFCO should be met and potentially exceeded in animals with liver dysfunction as long as the dietary protein is tolerated by the patient.[14,15] Protein is utilized for maintenance of lean muscle mass and protein synthesis and should exceed 18% dry matter basis (DM) in adult dogs (51.4 g protein/1000 kcal) and 26% in adult cats (65 g protein/1000 kcal) if no adverse effects are noted at these concentrations.[14] However, if HE is present, the protein quantity must be restricted.

Both ammonia and false neurotransmitters are produced from protein metabolism in the gastrointestinal tract. Liver dysfunction or a compromised portal circulation prevents normal nitrogen metabolism leading to increased circulation of ammonia and false neurotransmitters. Signs of HE ensue partially from measurable hyperammonemia but also from unmeasurable false neurotransmitters. Protein intake should be reduced compared to the current intake in any patient exhibiting HE. Restriction below the current intake may require restriction below AAFCO minimum recommendations for the appropriate life stage and/or the NRC-recommended allowance, unless the patient was currently consuming a high-protein diet. Restriction beyond that which prevents HE is not recommended to allow for maintenance of lean muscle mass and tissue function. Ideally, in patients requiring severe protein requirements, NRC minimums are still met (recommended allowance 10% for adult dogs on DM [25 g protein/1000 kcal] and 20% for adult cats on DM [50 g protein/1000 kcal]).[15] For puppies and kittens with HE, special care should be taken to use a diet that has undergone AAFCO feeding trials for growth to avoid deleterious effects of protein and other nutrient restriction in a growing animal.

The protein source and amino acid composition are also important to consider when choosing a diet for HE. Aromatic amino acids (AAA) are increased relative to branched-chain amino acids (BCAA) in patients with liver disease and are implicated in ammonia imbalances in patients with impaired liver circulation. They may act as substrates for production of encephalotoxins.[11,12,18,19] However, the use of diets with higher concentrations of BCAA versus AAA is controversial. Protein sources higher in BCAA than AAA are not necessarily beneficial for patients with liver disease, even if signs of chronic HE are present.[20] However, plant-based and dairy proteins, which are higher in BCAA, have been shown to prolong the time to development of HE and lessen their effects in dogs.[21,22] It is important to note that some plant-based protein, especially soy protein, is low in sulfur-containing amino acids, which are the precursors of taurine.

Even if protein restriction is necessary, meeting essential amino acid requirements set by AAFCO and/or NRC is important. In cats, arginine and taurine requirements in particular must be met despite protein restriction. Arginine deficiency in cats can cause rapid development of HE.[23] Taurine is essential for cats, and deficiency is associated with feline central retinal degeneration and dilated cardiomyopathy.[24–28] The AAFCO minimum concentrations for dietary arginine and taurine for adult cats are 1.04% DM (2.60 garginine/1000 kcal) and 0.1% (extruded diets, 250 mg taurine/1000 kcal) or 0.2% (canned diets, 500 mg taurine/1000 kcal).[14] In addition, some dogs on severely protein-restricted and/or plant-based diets may also require taurine supplementation to prevent taurine deficiency. Taurine deficiency in dogs is also associated with dilated cardiomyopathy.[29]Although there is no published dose for taurine supplementation for dogs with liver disease, whole blood and plasma taurine levels can be monitored to titrate supplementation, if necessary. If whole blood or plasma taurine concentrations indicate that a dog is taurine deficient, doses of 500–1000 mg crystalline taurine for small dogs and 1000–2000 mg for large dogs, dosed 2–3 times per day, have been published for dogs with cardiac disease.[30] Cats with dilated cardiomyopathy can benefit from 500–1000 mg taurine daily.[31] Feline central retinal degeneration associated with taurine deficiency, however, is irreversible. Protein-restricted commercial canine and feline therapeutic diets are supplemented with taurine; however, protein-restricted home-cooked diets should be supplemented with taurine to avoid the complications associated with taurine-deficient diets.

Vitamins and Minerals

The liver provides metabolism and/or storage for virtually all vitamins, copper, zinc, manganese, and other minerals. Deficiencies can be difficult to gauge until signs are present. Because they are water-soluble, most B vitamins are not stored in the body to a great extent. However, B vitamins are involved as cofactors in numerous metabolic reactions, including hepatic metabolism of macronutrients. B vitamins should be provided in the diet of patients who are eating a sufficient quantity of food, or they can be supplied parenterally if necessary.[4] For patients with liver disease, prolonged anorexia or hyporexia (if present) and reduced hepatic metabolic capacity make adequate intake of B vitamins essential.

Vitamin K deficiency is the most rapidly developing and readily detectable vitamin deficiency seen in dogs and cats with liver disease. Vitamin K-dependent clotting factors II, VII, IX, and X fall, and a coagulopathy results. Vitamin K deficiencies may be due to oral antibiotic therapy preventing bacterial production or chronic bile duct obstruction. Inadequate food intake can exacerbate vitamin K deficiencies. Signs of vitamin K deficiency usually resolve with supplementation.[11] If not, severe hepatocellular damage is assumed. Vitamin K_1 (phytonadione) should be supplemented at 1–5 mg/kg body weight per day if a deficiency is measured or expected.[5] While oral, subcutaneous, and intramuscular routes are generally well tolerated in the hydrated patient, the intravenous route of administration of Vitamin K_1 should be avoided to reduce the risk of anaphylaxis.[2,5]

Vitamins E and C are antioxidants that protect membrane phospholipids from oxidative damage from excess copper and iron and free radical generation in the damaged liver. Vitamin E is a

TABLE 1

Selected Supplements for Dogs and Cats with Liver Disease[a,8,26,27,36,40,41]

Supplement	Benefits	Conditions	Recommended Dose
Vitamin E	Antioxidant	General liver disease	50–400 IU/day
Vitamin C	Antioxidant, involved in production of L-carnitine and in the conversion of oxidized tocopherol (vitamin E) to active state	General liver disease, avoid in copper storage disease	500–1000 IU/day
L-Carnitine	Assists in uptake of fatty acids into mitochondria	HL	Cats, 250–500 mg/day
Zinc	Reduces liver copper accumulation and fibrosis; provides membrane stabilization, free radical scavenger, antioxidant, modulation of CYP450	Copper storage disease, general liver diseases	Copper storage disease: 15 mg/kg/day; general supplementation: 1–3 mg/kg/day
Taurine	Deficiency noted with protein-restricted diets, associated with dilated cardiomyopathy and central retinal degeneration (cats)	HE, when protein-restricted homemade diets are used (doses extrapolated from treatment of dilated cardiomyopathy)	500–1000 mg crystalline taurine for small dogs, 1000–2000 mg for large dogs, 2–3 times daily; 500–1000 mg for cats, daily
SAMe	Glutathione precursor, antioxidant via hepatic glutathione	Chronic hepatitis, HL, cholangiohepatitis, Heinz body anemia	20 mg/kg/day
Silymarin	Ameliorates hepatic injury, reduction of ALT and AST, free-radical scavenger, antioxidant	Toxin exposure, +/- hepatocellular necrosis	50–250 mg/day

[a]Not all supplements are safe for every patient.
ALT, alanine transaminase; AST, aspartate transaminase; HL, hepatic lipidosis; SAMe, S-adenosylmethionine

membrane-bound antioxidant, whereas vitamin C is an intracellular antioxidant that helps convert oxidized vitamin E back to its reduced, active form. Supplementing vitamins E and C may be beneficial as antioxidants in patients with liver disease. Recommended supplemental dosages of vitamins E and C are shown in **Table 1**. Vitamin E is fat soluble; therefore, excessive supplementation should be avoided. However, there is no published safe upper limit for vitamin E (alpha-tocopherol) for dogs or cats.[14,15] There is no published recommended allowance, dietary minimum, or safe upper limit for vitamin C, as it is not a required nutrient for dogs and cats.[1,14–16] Vitamin C should not be supplemented in cases of copper hepatopathy.[32]

Copper accumulation is known to occur more readily in several breeds of dogs, including Bedlington terriers, Dalmatians, and Labrador retrievers.[10,12,33–36] Copper is highly toxic when unbound to protein and causes oxidative damage to the liver. Accumulations are associated with a deficiency in the COMMD-1 gene in Bedlington Terriers, but one current study shows that excessive copper in the diets may contribute to copper-associated hepatopathies in other breeds of dogs, especially in Labrador Retrievers; however, this theory is not widely supported.[37] Initial treatment with copper chelators such as D-penicillamine will lower the liver copper concentration, but long-term management with a commercial or otherwise complete and balanced homemade reduced copper diet (<5 mg/kg DM copper or <1.25 mg/1000 kcal) is necessary for maintenance.[10,33,34] Foods such as liver, organ meats, shellfish, legumes, mushrooms, chocolate, nuts, and other high-copper foods, including some meats, should be limited or avoided.[10,33,34] Dietary copper restriction is not necessary in dogs without hepatic copper accumulation. Some researchers suggest that dietary copper concentration should not exceed 6–7.3 mg/kg DM per day for adult dogs.[37] However, the NRC does not currently have a published safe upper limit for dietary copper, and the AAFCO maximum for dogs is currently 250 mg/kg DM (71 mg/1000 kcal).[14,15] Copper processing from the small intestine to the liver requires the protein metallothionein.[10,33,34]

Metallothionein synthesis is also required for zinc metabolism. Supplementation of zinc alters metallothionein concentrations to reduce intestinal copper absorption.[10,38] Serum zinc concentrations may decrease in cases of severe liver disease because of reduced storage capability.[12,39] In addition, zinc supplementation has been advocated to reduce liver copper accumulation. Patients with severe hepatic copper accumulation require chelation with D-penicillamine for several months prior to starting zinc supplementation.[10,12] Zinc provides protection against some hepatotoxic agents via zinc-induced membrane stabilization, free radical

scavenging, antioxidant activity, maintenance of hepatocellular metallothionein, and modulation of specific cytochrome oxidases (i.e., cytochrome P450).[12,39] Zinc has been associated with reduced fibrosis as well. Zinc deficiencies result from reduced intake and impaired intestinal absorption. Liver disease causes abnormal protein binding and transport leading to increased urinary losses.[10–12] Practitioners should test serum zinc concentrations prior to supplementation to get a baseline, although the level detects toxicity, not therapeutic levels. It is recommended to retest in 7–14 days and then 2 mo and 6 mo after starting supplementation.[10,12] The recommended dosage for supplemental zinc in patients with non-copper-associated liver disease is 1–3 mg/kg elemental zinc per day.[12,40] This dose increases to 15 mg/kg (starting dose) of elemental zinc if using as a copper chelator in cases of copper hepatopathy. The dose can be decreased after 1–3 mo of therapy.[41] Zinc acetate or zinc gluconate are typically better tolerated than zinc sulfate.[41]

Manganese levels have been shown to be elevated in the whole blood of dogs with congenital portosystemic shunts. Impaired excretion of manganese is the likely cause of the elevation and has been shown to contribute to HE signs in humans with advance liver disease or shunts because of accumulations in the brain. MRI studies on humans have demonstrated brain lesions associated with manganese toxicities that cause psychosis, gait abnormalities, and cognitive deficits. Further research is warranted to determine the role that manganese plays in the development of HE in dogs.[42]

Nutritional Supplements

As liver function decreases, the risk for presence of free radicals and oxidative injury increases. Several supplements including vitamins E and C, L-carnitine (β-hydroxy-γ-trimethylaminobutyric acid), S-adenosylmethionine (SAMe), and silymarin (extract of milk thistle) can provide antioxidant effects, promote glutathionine replacement, and promote hepatocellular repair. Some of the many nutritional supplements recommended and/or marketed for patients with liver disease are shown in Table 1.

Probiotics have been used in humans with hepatobiliary disease, especially in cases of HE from cirrhosis and nonalcoholic steatohepatitis. While evidence-based medicine is lacking, current thoughts are that the probiotics can reduce urease-producing bacteria, thus reducing circulating ammonia levels. Also, alterations in the gut flora can lead to reductions in inflammatory-inducing bacterial translocation into the liver parenchyma. Probiotics may become more widely used in the near future in treating veterinary patients with hepatobiliary disease as well.[43,44]

Conclusion

Dogs and cats with hepatobiliary disease require specific dietary modifications with goals of avoiding clinical signs of liver disease while allowing for maximum regeneration of the liver and providing sufficient nutrients to patients. As a result, dietary recommendations for patients with liver disease depend on clinical signs and disease etiology, if known. Recommendations are patient specific and are based on the individual patient's clinical signs. For all patients, important goals include either maintaining body weight or achieving IBW in underweight patients. Several varieties of veterinary therapeutic diets exist to provide balanced nutritional sources specific to patients with liver disease. However, commercially available hepatic diets are protein restricted and may not be ideal for all patients with liver disease. In addition, patients with multiple problems that need to be managed nutritionally should be managed according to their specific problem set. In all cases, the diet that the individual patient consumes readily is paramount to ensuring the best opportunity for liver regeneration in the diseased state.

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