The Pharma Innovation Journal 2023; 12(1): 1352-1359

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(1): 1352-1359

www.thepharmajournal.com
Received: 14-10-2022
Accepted: 22-11-2022

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Nutritional management of liver diseases in dogs and cats

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Abstract
Liver diseases are common in canines and felines. The potential causes are numerous including viral, bacterial, and parasitic infections, toxins, cancerous processes, and drugs like phenobarbital, non-steroid anti-inflammatory drugs, and steroids. Treatment and prognosis of liver disease rely on the underlying cause. However, most of the cases can be successfully treated because of the incredible regenerative capacity of the liver. The treatment strategies target providing rest to the liver and minimizing the functions dealing with carbohydrates, proteins, fat, and drug metabolism. Successful management of the disease requires a proper understanding of hepatic metabolism and the nutritional process. Nutrients can influence the development and function of the gastrointestinal tract, and manipulation of diet can be exercised as a therapeutic strategy to be used alone or in combination with drug therapy to provide promising results. This article provides a review of hepatic diseases in canine and feline and their nutritional management.

Keywords: cats, dogs**,** liver diseases, nutraceutical, nutritional management

Introduction
Liver diseases are common in pets these days. They are occasionally diagnosed in cats but are a relatively common finding in dogs. Many vital functions, including the synthesis and metabolism of carbohydrates, protein, and fat are performed by the liver. Liver disease can affect the metabolism and usage of nutrients. It leads to problems with the metabolism and depot of nutrients and the breakdown of their potentially harmful by-products or toxins. The liver also plays a role in the production of red blood cells and factors needed for the normal clotting of blood. It is also a vital part of the immune system and detoxifies chemicals and drugs ingested by the body. As it has such essential functions, liver disease can result in some serious health consequences. Nutrition plays an indispensable role in assisting in supporting these patients, and while feeding a specially formulated diet, nutrition can prolong life too. In companion animals, common diseases of the liver include vascular anomalies, acute or chronic hepatitis, hepatic Lipidosis, Neoplasia, Toxicosis, and cholangitis.

Pets at most risk for liver disease
All breeds are susceptible to the disease however; few breeds are at an increased risk to develop the disease (Watson, 2017) [45]. They include Yorkshire Terriers, Cairn Terriers, Scottish Terriers, Malteses, Golden and Labrador Retrievers, Schnauzers, Poodles, Dobermann, Cocker spaniel, and German Shepherds. No breed predisposition was observed in cats; however, obese cats are more prone to a fatty liver disease called hepatic lipidosis. Younger animals are predisposed to portosystemic shunt (PSS, a specific genetic circulatory problem of the liver) which may result in nervous signs in severe cases.

Liver functions
Physiological functions of the liver which are vital comprise intermediary metabolism of nutrients (carbohydrates, proteins, and lipids), blood coagulation, storage, bilirubin, and xenobiotic (drug) metabolism (Michel, 1995) [25]. Thus, maintaining a healthy liver is a crucial factor for the overall health and well-being of pet animals.

Carbohydrate metabolism
The liver is the major site of gluconeogenesis, glycogenesis, and storage. Glycogen constitutes about 5-6% of the liver's fresh weight which is used for the synthesis of fatty acids or oxidized

for energy production. In dogs, around 40 to 70% of the glucose ingested in a meal is taken up by the liver from the portal circulation (Barrett *et al*., 1985) [5]. Meanwhile, the amount of glucose extracted by the feline liver is less as cats lack the hepatic enzyme glucokinase. The activity of glucokinase is governed by the presence of high glucose levels, and the lack of this enzyme in cats is thought to reflect the low direct contribution of dietary carbohydrates to the maintenance of serum glucose levels in this species. In summary, the liver plays a crucial role in regulating carbohydrate homeostasis and serum glucose levels by its ability to remove glucose from and release glucose into circulation (Michel, 1995) [25]. However, the relative significance of these mechanisms varies among different species. The liver dysfunction could lead to abnormal serum glucose levels resulting either in hypoglycemia or hyperglycemia.

Protein metabolism

The liver plays a crucial role in the synthesis and degradation of the protein. It is the source of many serum proteins, including transport proteins, acute phase proteins, and clotting factors. Ammonia is detoxified in the liver through urea synthesis. A healthy liver has a remarkable capacity to remove ammonia from the blood. Hyperammonemia occurs during hepatic dysfunction when the impaired ureagenesis cannot keep pace with ammonia genesis (Michel, 1995) [25].

Fat metabolism

The liver plays an indispensable role in lipid synthesis and transportation. Through the bile salts synthesis and secretion of bile, it also aids in the digestion and absorption of dietary fat. It is a prime site for cholesterol synthesis and the only site for ketogenesis in cats and dogs (Bruss, 1989) [4]. Commonly, glucose uptake by the liver in the absorptive state is used for long-chain fatty acid synthesis. These fatty acids are then packed into lipoproteins and liberated into systemic circulation. The liver can also take up free-fatty acids absorbed from the intestinal tract or liberated from adipose tissue in the fasting state. These fatty acids are then conveyed into mitochondria where they undergo oxidation for energy production, re-esterified into triglycerides, and released into the circulation or metabolized into ketone bodies. Imbalance in fatty acid uptake, synthesis, utilization, and release, resulting in lipid accumulation in hepatocytes are outcomes of hepatic dysfunction. Damage to the liver parenchyma or biliary obstruction can end up in decreased secretion of bile salts. Bile salts aid in lipid absorption through the emulsification of fats. As bile salts facilitate the absorption of long-chain fatty acids, one might think that decreased secretion of these salts would result in fat malabsorption. Nevertheless, the formation of the micelle is not essential for long-chain fatty acid absorption, and 30% to 40% of dietary triglycerides can still be absorbed in the complete absence of bile salts (Gallagher, 1965) [12]. Nevertheless, cholesterol and fat-soluble vitamin (A, D, K, and E) absorption still depend on micelle formation. Thus, decreased bile salt secretion results in the malabsorption of these nutrients.

Detoxification and excretion of metabolites

Even though detoxification and excretion of metabolites are not directly related to nutrition, these functions deserve consideration as the liver is the prime site of detoxification both of the endogenous by-products of the intermediary metabolism (e.g., ammonia) and of exogenous substances absorbed from the digestive tract. These exogenous substances include feed additives or metabolites of bacterial action on dietary components. Some investigators have suggested that consumption of commercial pet foods in the face of liver disease should be avoided because intestinal microflora can metabolize food additives into potent hepatotoxins, which may cause further hepatic injury, as the impaired liver does not inactivate them (Strombeck *et al*., 1990) [40].

Common liver diseases in dogs and cats

Hepatic encephalopathy (HE)

Hepatic encephalopathy is a metabolic disorder that develops secondary to liver disease (known as hepatopathy) leading to the accumulation of ammonia in the body due to the liver's inability to get rid of the substance. Also, it affects the central nervous system. The altered serum concentrations of one or more metabolites in hepatic disease or portosystemic shunts result in neurologic derangement. Hyperammonemia is mostly seen in patients with hepatic dysfunction and can cause a variety of nervous signs. It has been observed in humans and dogs; however, serum ammonia levels often do not correlate with the clinical severity of neurologic derangement. This observation has prompted a search for other potentially toxic substances or metabolic imbalances that may be at work in patients with hepatic encephalopathy. The most frequent cause of HE is portosystemic shunting (PSS). Although the pathophysiology is likely complicated, it is not fully understood (Salgado and Cortes, 2013) [37]. For dogs with PSS, it is advised to consume dietary protein that offers at least 2.1 g of CP/kg/d (Laflamme *et al*., 1993) [17]. Various studies, often involving canine models of liver disease, have implicated metabolites generated by gastrointestinal microbes and varied serum amino acid concentrations as accepted causes of hepatic encephalopathy. By-products of gut microbial metabolism include mercaptans that are synthesized from methionine and short-chain fatty acids (SCFA), which principally are the result of fiber fermentation in the colon. Both methionine toxicosis and abnormal serum amino acid levels have been observed clinically in small animals with neurologic signs.

Feline idiopathic hepatic lipidosis (IHL or HL)

Feline hepatic lipidosis is a common condition in cats that is characterized by the accumulation of large amounts of fat. It is a severe condition in which 50% of the hepatic weight is attributable to retained triglycerides. Cats that are older and obese are more vulnerable. Severe hepatocellular vacuolation with triglyceride distorts the cytosolic compartment and collapses canaliculi (Center *et al*., 1998) [6]. About 50% of cats have an underlying primary disease-causing inappetence. The disease is characterized by fatty infiltration of the liver, non-regenerative anemia, hepatic encephalopathy, jaundice, and liver failure (Armstrong and Blanchard, 2009) [1]. Possible causative mechanisms include starvation, relative arginine or carnitine deficiencies, and insulin resistance. Affected cats develop increased liver enzymes, particularly alkaline phosphatase activity, and are hyperbilirubinemia and jaundiced. Increased serum bile acid levels precede jaundice. Most cats develop abnormal erythrocyte morphology (irregular shapes, poikilocytes) with acanthocytes being the

most common. Many cats become hypokalemic, and some will develop hypophosphatemia which may result in hemolysis. Hypokalemia must be judiciously corrected as soon as possible because this electrolyte abnormality is associated with a poor prognosis. A unique difference in liver enzyme activity contrasting with other feline cholestatic liver disorders is the relative inactivity of g-glutamyl transferase compared with alkaline phosphatase. Whatever the cause, it is essential that early diagnosis should be made, and affected cats require aggressive nutritional and fluid support. In most cases, initial feeding is achieved using nasogastric intubation.

Copper-associated hepatic toxicosis

Copper-associated hepatic toxicosis occurs in dogs, mainly because of two reasons. The first being a hereditary defect in copper elimination, which causes accumulation and the second one occurs as secondary to primary liver disease. Copper is known to be hepatotoxic, once significant intracellular concentrations develop. In this condition, there will be a progressive accumulation of copper in the lysosomes of hepatocytes. It leads to chronic hepatitis. Dietary therapy (i.e., feeding low copper diets) is unlikely to have much impact on patients with copper storage disease that are showing clinical signs of hepatic dysfunction because these dogs already have increased copper concentration in their liver. Instead, copper chelator therapy is recommended. Hepatic copper concentrations in Labrador dogs can be reduced by feeding them low-copper diets (Hoffmann *et al*., 2009). Chelator therapy not only prevents the absorption of dietary copper but also promotes the loss of endogenous copper, thus gradually reducing the amount of copper stored in the liver. It is possible that a restricted copper diet might be useful in managing dogs with hereditary defects of copper metabolism if such a diet is initiated early in life.

Diet for liver disease

In patients with advanced liver disease, malnutrition is a common finding and has been demonstrated as an independent risk factor for predicting clinical outcomes in those with chronic liver disease (Qiao *et al*., 1988) [30]. It is essential to recognize that weight loss commonly occurs in the face of usual dietary intake, suggesting that factors other than caloric intake are involved in the malnutrition of these patients. Potential reasons for malnutrition in animals with liver disease include: (1) anorexia, nausea, and vomiting; (2) impaired nutrient digestion, absorption, and metabolism; (3) increased energy requirements, and (4) accelerated protein catabolism with impaired protein synthesis.

Most pet owners are interested in providing nutritionally balanced commercial pet foods and some are offering homemade recipes for their pets. Formulating homemade diets for pets with the hepatic disease is not an easy task. It requires the knowledge about nutritional requirements of pets, the composition of the available ingredients, and the formulation process. The diet should be palatable with an adequate amount of good quality protein and other micronutrients. Some homemade recipes for dogs and cats with liver diseases were given in Table 1.

Table 1: Home-made recipes for dogs and cats with liver diseases

Species	Recipe	Nutrient composition/recommendations	Reference
Canine	3 large eggs 1 cup of rice 2 teaspoon corn oil 5g Dicalcium phosphate 1/3 teaspoon iodized KCl	Energy – 1000 kcal Protein – 13% Fat – 25% Carbohydrate – 62%	Mitchel, 1995
Feline	4 large eggs ¼ cup rice ¼ teaspoon corn oil 3g dicalcium phosphate 1/8 teaspoon iodized KCl	Energy – 500 kcal Protein – 22% Fat – 45% Carbohydrate – 33%	
Canine	1 hard-cooked egg 2½ cups cooked rice 2 tablespoons sunflower oil ¼ teaspoon $CaCO_3$ ¼ teaspoon NaCl	If hepatic encephalopathy is present or suspect	Bauer, 1989
Feline	2 hard-cooked eggs 2 cups cooked rice 1 tablespoon sunflower oil ¼ lb. liver 1 teaspoon $CaCO_3$	For initial liver failure cases (having high digestibility, moderate salt, and protein)	

Nutritional management of liver diseases in pets

Energy requirement

In liver patients, the energy requirements may be increased above the normal estimated daily energy requirements (DER) because of the catabolic nature of the liver disease. Acute inflammatory liver disease patients are more catabolic and require higher maintenance energy requirements than those with cirrhosis. In dogs with vacuolar, inflammatory, or toxic hepatopathies there are no guidelines for estimating energy needs. The provision of adequate daily energy intake to allow for protein synthesis and prevent tissue catabolism with subsequent ammonia genesis is essential.

Most hospitalized dogs are fed at their resting energy requirements (RER). It is very difficult to calculate the energy requirements of the liver patient due to decreased activity levels. Most liver patients are underweight due to reduced appetite (hyporexia) and require an energy-dense diet to reduce the quantity of food necessary to meet DER. In this case, a diet with increased fat and decreased fibre content can increase palatability and energy density, which makes it easier to meet DER and also maintain body weight and body condition score (BCS) (Norton *et al*., 2016) [28]. Liver patients who have been anorexic for a long period of time switch to using fatty acids and ketone bodies for energy instead of

glucose (Saker and Remillard, 2010) [36]. So, a high-fat diet can be beneficial in these patients because of the metabolic shifts that occur during starvation. In addition to providing an energy-dense diet, heating the meal or hand feeding may improve palatability and appetite and appetite stimulants can also be used to meet its DER.

Protein

In liver patients, protein is needed for the regeneration of hepatic tissue and also to maintain the nitrogen balance. Protein has to be restricted in the diet only when signs of hepatic encephalopathy are present. In animals with liver dysfunction, protein requirements defined by the NRC and AAFCO should be fulfilled and even surpassed, as long as the patient tolerates the dietary protein. If excess protein is provided in the diet, gets deaminated, where the carbon chain is utilized for energy/ storage and nitrogen is converted to ammonia, which reaches the liver where it is converted to urea. Finally, the urea is excreted through the kidneys. But in liver dysfunction, the conversion of ammonia to urea is decreased leading to increased blood ammonia concentration.

In liver disorder, protein requirement may increase due to the increased protein turnover (Ruaux, 2017) [34]. If no deleterious effects are observed, protein should surpass 18% dry matter basis (DM) in adult dogs (3-4g/100kcal) and 26% in adult cats (6-8 g/ 100 kcal), for the maintenance of the lean muscle mass and body protein synthesis (AAFCO, 2013) [2]. Highly digestible proteins, particularly those derived from vegetables and milk, have been found to ease canine HE symptoms (Proot *et al*., 2009) [29]. Metabolism of protein in the gastrointestinal tract produces ammonia and false neurotransmitters. Liver dysfunction or impaired portal circulation affects normal nitrogen metabolism leading to increased ammonia and false neurotransmitters in circulation, which can induce the signs of HE.

When choosing a diet for HE patients, the source of protein and amino acid content are also crucial factors to be considered. In some severe cases, protein restriction may be necessary with providing all the essential amino acids as per the standards of AAFCO and NRC is important. In cats, supplementation of arginine and taurine is necessary despite of protein restriction. In cats, arginine deficiency can lead to the development of HE (Morris and Rogers, 1978) [26]. Reassessment of the patient's condition after 3-4 weeks and further increase or decrease in protein concentration is needed based on the patient tolerance to diet and clinical response to therapy.

Digestible carbohydrates

The liver plays important role in carbohydrate metabolism and is the prime site of gluconeogenesis and glycogenesis. Usually, excess dietary glucose is stored as glycogen in the liver and muscle and is utilized for fatty acid synthesis and energy production via glycolysis. In liver disorders, the glucose metabolism will get altered which results in either hypoglycemia or hyperglycemia. The requirement of dietary soluble carbohydrates can be higher in patients with cirrhosis, hepatic failure, and congenital portovascular anomalies to maintain adequate glucose levels and in hepatic lipidosis cases, the dietary soluble carbohydrates should be limited to prevent diarrhea, abdominal pain, and hyperglycemia (Center, 1998) [6]. Frequently feeding small meals may help to prevent the hypoglycemic condition in these patients. Highly digestible carbohydrates such as white rice should be included in the diet of liver patients with a tendency to become hypoglycemic (Norton *et al.*, 2016) [28]. In liver patients, the energy that is derived from soluble carbohydrates should not exceed 45% of total metabolizable energy (Rutgers and Biourge, 2006) [35].

In hepatic encephalopathy, lactulose administration is considered the treatment of choice. It is a synthetic disaccharide that is principally hydrolyzed to lactic and acetic acids by colonic bacteria (Lieberthal, 1988) [19]. Lactulose appears to exert its beneficial effects by (1) Lowering colonic pH with subsequent trapping of ammonium ions; (2) inhibiting ammonia generation by colonic bacteria through catabolite repression; (3) decreasing intestinal transit time due to its cathartic properties; and (4) suppressing bacterial and intestinal ammonia generation by providing a carbohydrate source.

Dietary fibre

Dietary fibre has many advantageous actions though it reduces the calories in the diet. A soluble fibre derived from pectin, gums, mucilages, and psyllium is fermented in the colon. This type of fibre has a high capacity to retain water, thus increasing faecal bulk. Various other influences imparted by soluble fibre ingestion include an increase in the unstirred water layer adjacent to the enterocyte, an ability to alter intestinal transit time, to bind enteric toxins, to stimulate enteric IgA production, and alter the resident enteric flora. Alteration of gut flora by favoring acidophilic organisms (e.g., Lactobacillus) may minimize enteric ammonia production, and increase the fermentation of fibre and lactulose, as well as beneficial SCFA production. It binds bile acids in the intestinal tract and promotes their removal. Fermentation of soluble fibre generates short-chain fatty acids, which impair intestinal uptake of ammonia by decreasing the colonic pH, similar to the theoretical actions of lactulose. The decreased pH converts ammonia to ammonium, which is less absorbable (ion trapping) and more likely to be excreted in the faeces. The inclusion of insoluble and soluble fibre enhances colonic transit and helps prevent constipation, giving toxins less time to be absorbed from the colon (Meyer *et al*., 2010) [23]. Soluble fibre can be used to soften the stool, although high amounts can cause diarrhea. Some soluble fibre sources, like sugar beet pulp and guar gum, also appear to decrease the use of amino acids as a gluconeogenesis substrate, by increasing the use of SCFA (Wambacq *et al*., 2016) [44].

Dietary fat

Recommendations of dietary fat for those 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 increased fat content can increase palatability for patients with reduced appetites while increasing calorie density, thus making it easier to meet energy requirements. Dietary fat restriction is usually not needed for most liver disease patients unless pronounced cholestasis or fat malassimilation is present. Fats provide Essential Fatty Acids (EFA) and have a protein-sparing effect (Meyer *et al*., 2010) [23]. Also, because fat is an energy-dense nutrient, dietary fat can be beneficial for underweight patients. However, it is contraindicated to utilize high-fat diets in dogs with a history of pancreatitis, in cats and dogs with

hyperlipidemia, and with severe cholestatic disease. The requirement of fat for dogs and cats with various diseases is mostly unknown, and there is variation among different patients.

Vitamins and minerals

The liver is the main site for the metabolism and storage of almost all vitamins, and minerals like copper, zinc, manganese, and others. Therefore, deficiencies are diagnosed after the appearance of signs. Vitamin and mineral deficiencies may occur due to inadequate intake, malassimilation, and decreased hepatic reserves. Water-soluble vitamins, such as thiamine, riboflavin, niacin, folic acid, and cobalamin have a little reserve. A multivitamin preparation is often recommended for liver diseases; water-soluble vitamins generally have low toxicity.

Water-soluble vitamins

For patients with liver disease, prolonged anorexia or hyporexia (if present) and reduced hepatic metabolic capacity make the adequate intake of B vitamins essential. Thiamine is an essential coenzyme in intermediate carbohydrate metabolism, functioning as a coenzyme in the pentose-phosphate pathway (transketolase) and tricarboxylic acid cycle (pyruvate decarboxylase and a-ketoglutarate). Deficiency induces a syndrome known as Wernicke's encephalopathy, which is easily avoided by supplementation with a balanced vitamin formula (Reuler *et al*., 1985) [32]. Thiamine (vitamin B1) supplementation is recommended in patients with hepatic diseases, especially in cats as they are more sensitive to thiamine deficiency. Thiamine deficiency signs are similar to that of hepatic encephalopathy. Thiamine Dosage for cats is 10–25 mg IM and for dogs is 50–250 mg/dog IM or PO, given until signs resolve (Ramsey *et al*., 2017) [31]. Cobalamin (vitamin B12) is likely to be deficient in cats with concurrent pancreatitis or intestinal malassimilation (Simpson, 2015) [38]. Subnormal concentrations of vitamin B-12 have been demonstrated in some cats with cholangiohepatitis associated with chronic inflammatory bowel disease. Low concentrations of cobalamin have been documented in cats with hepatic lipidosis. Degenerative liver disease has been diagnosed in young Beagles as a result of hereditary cobalamin malabsorption due to tubulin gene mutation (Kook *et al*., 2014) [16]. Injectable vitamin B-12 (1 mg every 7–28 d) has successfully repleted plasma vitamin concentrations. Vitamin C should be supplemented in the diet of dogs and cats with hepatic disease, as lower plasma concentrations of ascorbate are present in these patients (Strombeck *et al*., 1983) [39], and dogs will tolerate doses of 25mg/kg body weight PO per day. Vitamin C also acts as a pro-oxidant when present in high concentrations in the presence of metals such as iron and copper, so excessive vitamin C supplementation should be avoided in dogs having copper-associated hepatotoxicity.

Fat-soluble vitamins

The uptake of fat-soluble vitamins (vitamins A, D, E, and K) can be reduced by any disorder that decreases bile acid flow (e.g., cholestasis), enterohepatic bile acid circulation, or intestinal fat absorption. Vitamins A and D are stored in moderate to large amounts and are not commonly deficient; vitamin K and E deficiencies are more common. Liver vitamin K stores are rapidly depleted in liver disease, although intestinal bacteria producing vitamin K can maintain concentrations for about a month (Marks, 2012). Bleeding in hepatic disease is more common due to the decreased synthesis of prothrombin-complex clotting factors, as this function is lost before vitamin K stores are depleted (Mammen, 1994) [21]. If indicated, vitamin K1 is given at 1–3 mg/kg SQ or 5 mg/kg PO. Overdosing should be avoided in cats, as it can cause hemolysis and hepatic necrosis (Ramsey *et al*., 2017) [31]. Vitamin E (tocopherol) acts as a natural antioxidant, and it protects the hepatocyte membrane phospholipids from mitochondrially derived oxidative free radicals or reactive oxygen species (Vandeweerd *et al*. 2013) [41]. Vitamin E supplements have been recommended for hepatobiliary diseases (e.g., cholestatic and neuroinflammatory hepatopathies) in which anti-oxidant activity may be of benefit. In such diseases, a dose of alpha-tocopherol acetate @ 15 IU/kg/d PO, has been recommended for dogs and cats.

Minerals

Copper accumulation is known to occur in several dog breeds, including Bedlington terries, Dalmatians, and Labrador retrievers. Cu is highly toxic when unbound to protein and can cause oxidative damage to the liver. In this case, copper chelators like D- penicillamine will lower the liver-Cu concentration (Fietan *et al*., 2014) [9]. Dietary copper restriction is also needed in these patients. There is clear evidence that Zinc (Zn) deficiency is prevalent in liver diseases (Riggio *et al*., 1991) [33]. Excess zinc inhibits the intestinal absorption of copper and its deposition in the liver (Fischer *et al*., 1983). Zinc stimulates the transcription of the copper-binding protein, metallothionein, in the gastrointestinal tract and hepatocytes, resulting in increased binding. Metallothionein has a greater affinity for copper than for zinc, so copper is bound in the enterocytes and excreted into the feces with desquamated epithelial cells. Zn should be supplemented as Zn gluconate or Zn citrate @ 5mg/ kg BW/ day. Zinc protects 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). Hypokalemia is a common finding in canine hepatic cirrhosis and feline hepatic lipidosis. In such cases, serum potassium concentrations should be monitored and supplemented whenever there is a need for patients. Hypokalemia can prolong anorexia and worsen hepatic encephalopathy. Manganese (Mn) levels are elevated in the whole blood of dogs with congenital portosystemic shunts. Impaired excretion of Mn will be the main cause of the elevation. Elevated levels of manganese will cause signs of HE due to accumulation in the brain.

Nutraceuticals

Many nutraceuticals have been used in dogs and cats with liver disorders to aid in support or improvement of liver health. Therapeutic hepatoprotectants including prescription drugs and nondrug dietary supplements have the potential role in the treatment of liver diseases in dogs and cats. Some commonly used hepatoprotective dietary supplements (nutraceuticals) include SAMe, Ursodeoxycholic acid, Silymarin, L-Carnitine, and N-acetyl Cysteine.

S-Adenosyl-L-Methionine (SAMe)

Dietary methionine is converted to SAMe with the help of MAT1 (methionine adenosine transferase 1) and ATP. It is essential for transmethylation, transsulfuration, and aminopropylation, which are some of the significant biochemical hepatic pathways that may be impaired in disease (Chandler *et al*., 2019) [8]. A decrease in methionine clearance, glutathione (GSH), and taurine production occur as a result of impairment in transsulfuration (Werge *et al*., 2021) [47]. Glutathione and taurine have hepatic antioxidant and detoxifying actions. Experimental studies and clinical trials in humans, dogs, and cats have shown that parenteral and oral administration of SAMe can increase GSH in RBCs and hepatic tissue (Wallace *et al*., 2002; Viviano and Vander Wielen, 2013) [43, 42], but how SAMe accesses hepatocytes remains controversial. When used, it will have cytoprotective, analgesic, and anti-inflammatory actions. A dose rate of 20mg/kg/day on an empty stomach will significantly increase plasma SAMe concentration in dogs and cats.

Silymarin (silibinin)

Silybum marianum, or milk thistle, is commonly used for the treatment of humans and animals with hepatic failure. Silymarin is a standardized extract of milk thistle fruits and seeds containing at least seven flavonolignans (including silibinin, iso-silibinin, silychristin, iso-silychristin, and silydianin) and one flavonoid (taxifolin). Silibinin is the predominant and most biologically potent compound in silymarin, composing 50–70% (Loguercio and Festi, 2011) [20]. Studies have indicated that silymarin has antioxidant, anti-inflammatory, and antifibrotic activities, and also promotes choleresis, enhances protein synthesis, inhibits hepatotoxin binding, increases GSH concentrations, and chelates iron (Hackett *et al*., 2013) [13]. A suggested dose of 50-250mg/day; is recommended in dogs and cats with liver diseases. The bioavailability of silymarin is very low when consumed PO, but can be increased by a complexed with phosphatidylcholine (Webb *et al.*, 2012) [46].

L-Carnitine

L-Carnitine (3-hydroxy-4-N-trimethylaminobutyrate) is a conditionally essential and vitamin-like nutrient involved in intermediary metabolism, in which it plays a crucial role in carbohydrate and fat metabolism. For the transport of long-chain fatty acids across the mitochondrial membrane into the mitochondrial matrix for β-oxidation, carnitine is a requisite cofactor. Also, it eliminates potentially toxic acyl groups from cells and equilibrates ratios of free CoA/ acetyl-CoA between the cytoplasm and mitochondria. Supplementation of dietary L-carnitine in obese cats may decrease the risk of hepatic lipidosis (HL), and may aid in the treatment of HL as well (Ibrahim *et al*., 2003) [15]. L-carnitine has been recommended for the management of cats with HL at an oral dose of 250 to 500mg/day per cat.

N-Acetyl cysteine

N-acetyl cysteine (NAC) is a formulation of the amino acid L-cysteine. It is marketed as a nutritional supplement that has hepatoprotective properties. NAC is potentially favourable for liver disease as it provides sulfhydryl groups and is converted into metabolites capable of stimulating GSH synthesis, promoting detoxification, improving vascular tone and liver mitochondria energy metabolism, and acting directly as free radical scavengers (Vandeweerde *et al*., 2013) [41].

Probiotics

Probiotics are used in humans with the hepatobiliary disease, especially in cases of HE from cirrhosis and non-alcoholic steatohepatitis. The probiotics can reduce urease-producing bacteria, consequently reducing circulating ammonia levels. Bacterial translocation from the digestive tract is a crucial mechanism in the development of infections. Probiotics cause modifications in the gut flora, which lead to reductions in inflammatory-inducing bacterial translocation into the liver parenchyma. Probiotics might reduce intestinal bacterial overgrowth, improve immunological host defenses, increase neutrophil phagocytic function, and inhibit enter invasive action of natural gut microbes (Gratz *et al*., 2010) [11]. They have been proposed to reduce the risk of a spontaneous infection relating to gut translocation. Probiotics can reduce intestinal permeability, bacterial translocation, and endotoxemia in both animal models and human trials, which is crucial for preventing problems from liver cirrhosis and infection post-liver transplantation (Lata *et al*., 2011) [18]

Conclusion

From the preceding discussion, it should be clear that no single diet will best suit the nutritional and clinical needs of all patients with liver disease or even those with one specific type of hepatic dysfunction. With a few exceptions, the nutrient requirements of dogs or cats with liver disease will be at least as high as those of a clinically normal animal (healthy animal). The requirements for protein (except in HE) and various micronutrients may be higher in liver disease than in the normal state. The early identification and resolution of the factors causing hepatic insult are integral to the successful repair and regeneration of the hepatocyte. Nutritional management is frequently delayed in small animals with hepatic disease due to insidious onset and lack of understanding of pathophysiologic mechanisms. Also, depending on the patient's nutritional status and underlying liver disorder therapeutic diets may need to be modified. Sufficient fat and carbohydrate must be provided to prevent the catabolism of protein for energy needs and consequent ammonia formation. Although nutritional therapy plays a supportive role in the management of most hepatic diseases, it is the primary treatment for hepatic encephalopathy and feline idiopathic hepatic lipidosis.

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