

The Canine Liver



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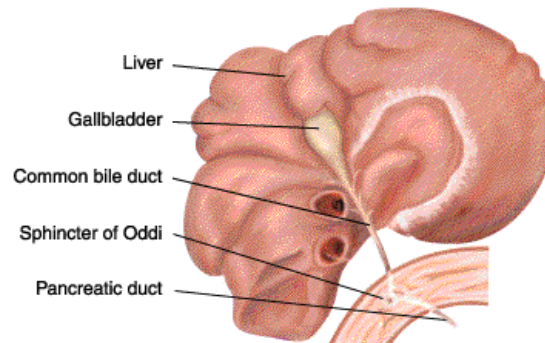
Key Points

- **Dogs may develop a range of inflammatory and non-inflammatory liver diseases, the most commonly being non-infectious inflammatory diseases**
- **The liver performs many vital functions with respect to nutrient digestion and metabolism, detoxification and excretion, hematology and coagulation, and hormonal balance**
- **Dietary management plays an important role in the overall treatment of dogs with liver disease and is designed to support liver function, irrespective of the type of disease diagnosed**
- **Dietary objectives are**
 - **To provide sufficient energy to maintain body weight with an optimal balance of protein, fat and carbohydrates**
 - **To balance protein intake to avoid hepatic encephalopathy and supply sufficient good quality protein for hepatocyte repair**
 - **To support liver function by supplementing zinc and restricting copper, and supplying fiber to avoid glucose intolerance**
 - **To manage hepatic encephalopathy by**
 - **Moderately restricting protein intake**
 - **Providing soluble and insoluble fiber**
 - **Providing adequate levels of zinc**

Nutritional support plays a key role in the management of hepatic insufficiency. The liver obtains more than 50% of its blood supply and the majority of its nutrients from the portal vein, which drains directly from the gastrointestinal tract. Manipulation of the nutrient content can therefore have a profound effect on the exposure of the liver to nutrients, hormones, bacterial products, and toxins and therefore improve its ability and capacity for regeneration and compensation.

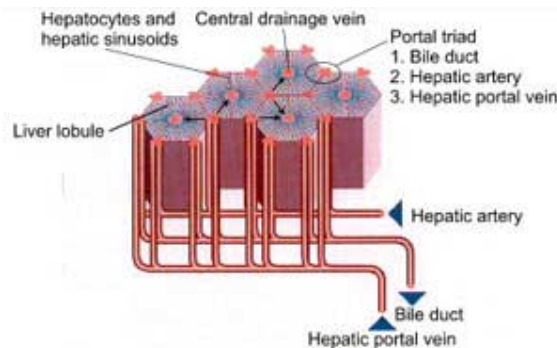
ANATOMY

The liver of the dog is partly covered by the rib cage, its cranial surface lying close to the diaphragm. The liver consists of three lobes, the central and a left and right lateral lobe. The *porta* is the place of entrance of the portal vein, the hepatic artery, and the nerves, as well as the place of exit of the hepatic ducts and lymphatic vessels.



The gallbladder collects the bile from the liver via the cystic and the hepatic ducts and joins the small intestine through the bile duct, an inch or so away from the *pylorus* of the stomach.

The liver receives blood from the intestinal tract via the portal vein, which is then delivered to the vena cava through the hepatic vein. The liver therefore receives all materials absorbed from the gastrointestinal tract except for some lipid which passes through the mesenteric lymphatics as chyle.



The histologic unit of the liver is the lobule. In cross-section, the lobule appears as a hexagon with the central vein (a branch of the hepatic vein) at the center and the portal triad at the corners. The portal triad consists of branches of the portal vein, the hepatic artery and the bile duct. This lobular pattern is a result of the hydrodynamics of the blood flow through the liver.

FUNCTION

The liver performs many vital functions with respect to nutrient digestion and metabolism, detoxification and excretion, hematology and coagulation, and hormonal balance.

Carbohydrate Metabolism

Carbohydrates are a useful source of energy, and the liver plays a key role in the carbohydrate metabolism including:

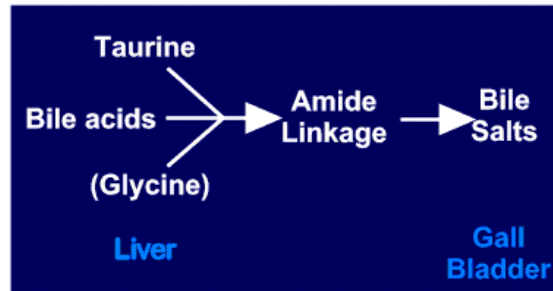
- Gluconeogenesis
- Control of glucose levels and glycogen metabolism and storage
 - Glycogen depletion and inadequate gluconeogenesis may lead to fasting hypoglycemia, but this is uncommon due to the large hepatic reserve for maintaining euglycemia.

Hypoglycemia may be seen with severe acute liver failure, large neoplasms (especially hepatoma), or congenital portosystemic shunts.

Lipid Metabolism

The liver performs a key role in the fat metabolism of the dog including synthesis of fatty acids, cholesterol, and triglycerides and the excretion of cholesterol and bile acids.

The implications of an abnormal lipid metabolism are still largely unknown. Total serum cholesterol may be increased by extrahepatic bile duct obstruction, while it may be decreased in severe hepatocellular failure or portosystemic shunts.

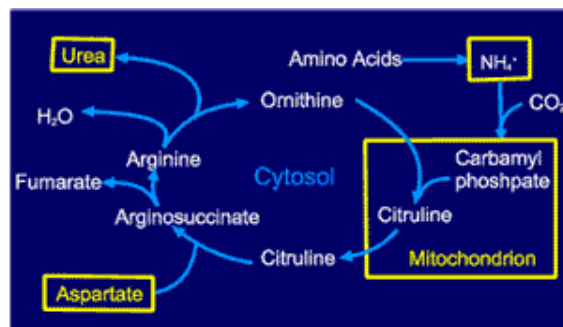


The role of taurine in bile salt productions

Protein Metabolism

The liver is key to the dog's protein metabolism, including:

- Synthesis of proteins (e.g., albumin)
 - The reduced synthesis of albumin in chronic liver disease may result in hypoalbuminemia. Other mechanisms of decreased albumin production include anorexia and malnutrition since protein synthesis strongly relies upon the availability of amino acids, tryptophan in particular. Intestinal or renal protein loss may further lower the serum albumin levels, or levels may appear reduced if the serum volume is increased (e.g., in portal hypertension with ascites). Serum albumin levels are therefore an insensitive index of hepatic function.
 - Monitoring serum albumin levels is, however, important for the dietary management, since it also gives an indication of the patient's overall nutritional status, particularly in states of chronic malnutrition.
- Regulation of amino acid metabolism
- Urea synthesis
- Detoxification of ammonia
 - Hyperammonemia is one of the characteristics of hepatic encephalopathy (HE). Ammonia is generated from the catabolism of proteins, nucleic acids, and urea. Most exogenous ammonia is produced in the colon through the degradation of dietary amines and the action of bacterial ureases on urea, after which it is absorbed into the portal blood and converted into urea in the liver by the Krebs-Henseleit urea cycle.



Urea cycle

- In patients with extra- or intrahepatic shunts and thus abnormal blood flow to the liver or, less commonly, with severe parenchymal damage, ammonia is not detoxified and enters the systemic circulation. Ammonia is neurotoxic, but its exact role in the pathogenesis of HE is controversial.

Vitamin Metabolism

The liver is key in the vitamin metabolism, responsible for the synthesis, storage, and activation of the vitamins A, B, D, E, and K.

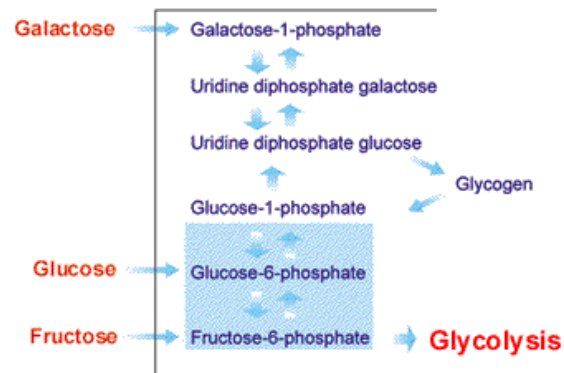
Hormone Metabolism

The liver also plays a crucial role in the metabolism of many hormones and is responsible for the degradation of peptide and steroid hormones.

Storage Function

The liver plays a key role in the storage of many nutrients and metabolites including:

- Vitamins
- Lipids
- Glycogen
- Copper
- Iron
- Zinc
- Blood



Conversion of galactose, fructose, and glucose into glucose-6-phosphate by the liver

Digestive Function

The liver plays a key role in the synthesis of bile acids and controlling enterohepatic circulation and has therefore important digestive functions.

Detoxification and Excretion

The liver is also crucial for the detoxification and excretion of a number of substances including:

- Bilirubin
- Ammonia
- Copper
- Cholesterol
- Steroid hormones

CLINICAL DISORDERS

Clinical signs are usually minimal in early stages of the disease, but become more apparent as the disease develops. Signs such as ascites, jaundice, and hepatic encephalopathy usually imply advanced disease and poor prognosis.



Dog with congenital portosystemic shunt showing signs of depression

Possible Clinical and Physical Findings in Liver Disease		
<ul style="list-style-type: none"> • Depression • Anorexia • Weight loss • Vomiting 	<ul style="list-style-type: none"> • Diarrhea • Polyuria/polydipsia • Bleeding tendency • Jaundice 	<ul style="list-style-type: none"> • Ascites • Encephalopathy • Hepatomegaly/microhepatica • Painful liver

Primary liver disease in the dog can be classified histologically into inflammatory and noninflammatory diseases. The largest category are noninfectious inflammatory diseases (chronic hepatitis and cirrhosis), followed by hepatic neoplasia, toxic hepatopathy, and portosystemic shunts.

Chronic Hepatitis

Chronic hepatitis includes a range of inflammatory liver diseases resulting from a variety of different causes, most of which can lead to cirrhosis (see below). Often, the etiology is not determined; metabolic, congenital/hereditary, infectious, toxic, and immune-mediated factors have been implicated.

Copper-associated chronic hepatitis has been documented in a number of breeds as an inherited etiology, while the increased incidence of specific types of chronic hepatitis in certain breeds suggests a genetic predisposition.



Lateral cranial abdominal radiograph of a dog with chronic active hepatitis (Source: P. Watson)

Infectious Liver Disease

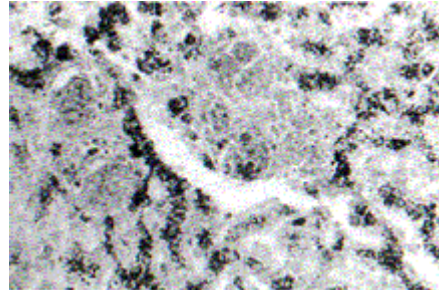
Infectious canine hepatitis is a disease rarely seen in the past decade since most dogs are vaccinated.

Leptospirosis remains a threat even in vaccinated dogs. Routine vaccinations help to protect against the two most common serovars, *L. canicola* and *L. ichthohemorrhagice*; however, several other serovars exist that may infect dogs and induce disease regardless of their vaccination status. This infection should be suspected in dogs with acute liver failure, particularly when accompanied by acute renal failure.

Nonspecific bacterial invasion of the liver (suppurative cholangiohepatitis) may occur due to ascending biliary infections (often *Escherichia coli*) or as a result of trauma and/or hypoxia, allowing proliferation of bacteria that are normally present in the liver.

Copper-Associated Chronic Hepatitis

Copper accumulation associated with chronic hepatitis may result either from a primary defect of copper metabolism, as seen in Bedlington Terriers or West Highland White Terriers, or from secondary copper retention as a result of altered normal biliary copper excretion.



Dark-stained copper granules in the liver of a Bedlington Terrier

Immune-Mediated Hepatitis

Immune-mediated mechanisms may play a role in many cases of chronic hepatitis. It is thought that nonspecific damage to hepatocytes may result in the release of liver antigens, leading to the formation of antibodies against these. These antibodies can then damage intact hepatocytes and lead to hepatitis.

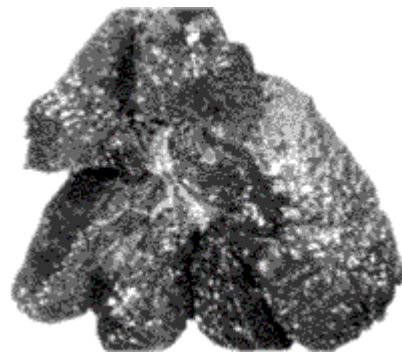
Other Forms

There are other forms of chronic hepatitis with unknown etiology. Some of these forms are breed-related and there may be certain metabolic abnormalities underlying such diseases.

Cirrhosis and Fibrosis

The end-stage of many liver diseases is cirrhosis, which is characterized by disruption of the normal liver structure by regenerative nodules and fibrosis. Patients with chronic liver failure usually show clinical signs and biochemical changes. A biopsy is generally necessary to differentiate end-stage failure from potentially reversible liver diseases.

Treatment is symptomatic and the prognosis is poor. Fibrosis usually occurs as a component of chronic inflammatory disease and/or cirrhosis to repair hepatic injury.



Cirrhotic appearance of the liver of a 7-year-old female Labrador Retriever with chronic active hepatitis

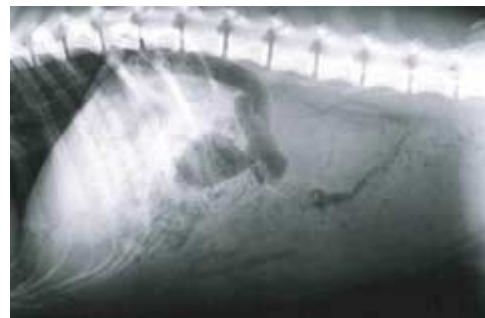
Toxic Liver Disease

Many chemicals, including drugs, anesthetics, or biologic toxins can damage the liver, even though the actual cause is often never identified. Hepatotoxic changes may also be seen following on from hypoxemia due to severe anemia, acute circulatory failure, shock, or thrombembolism. The clinical signs may vary from mild degenerative changes to full-blown acute hepatic failure, often with an acute clinical onset.

Prognosis for full recovery depends on the severity of the insult and is poor for severe hepatic necrosis. Patients that do not die from acute liver failure often recover with supportive care.

Congenital Portosystemic Shunts

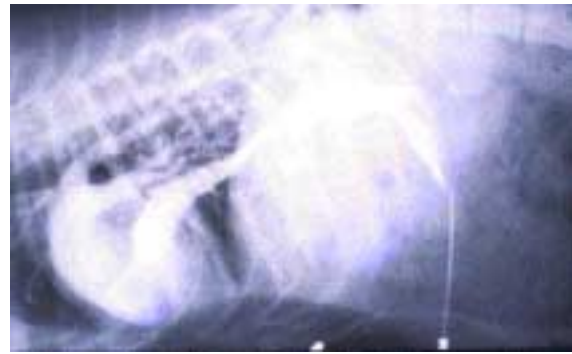
Congenital portosystemic shunts can be seen as intra- or extrahepatic shunting of the normal blood flow. The main clinical signs are those of hepatic encephalopathy, usually appearing at an early puppy age, as well as stunted growth and poor body development. Laboratory findings usually consist of microcytosis, and increased blood ammonia and bile acid concentrations. Dietary management is advisable before and after surgical correction of the shunting, as well as in patients where surgical ligation is not possible.



Lateral abdominal radiograph of a congenital portosystemic shunt



Ultrasound scan of the liver with an intrahepatic congenital portosystemic shunt
(Source: P. Watson)



Lateral cranial abdominal radiograph of extrahepatic congenital portosystemic shunt
(Source: P. Watson)

Neoplasia

Lymphosarcoma is perhaps the most common primary hepatic tumor. Other forms of primary hepatic neoplasia such as hepatomas, hepatocellular carcinomas, and cholangiocellular carcinomas are less common and more likely to occur in older dogs. Metastases from carcinomas or sarcomas from the pancreas, spleen, gastrointestinal tract, bone marrow, mammary, or adrenal and thyroid glands may also be seen.

The clinical signs are nonspecific and vague, but liver imaging may reveal hepatomegaly or hepatic masses. Dogs with hepatic tumors may show hypoglycemia, which is thought to be due to excessive glucose consumption and the release of insulin-like substances by the tumor.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) comprises a series of neurologic signs, which develop as a result of portosystemic shunting or a significant loss of liver function (60-70%) in acute or chronic liver disease. The clinical signs vary and can be clinical or subclinical. The exact pathogenesis remains controversial, and it is believed that a number of factors are involved.

There are a number of nitrogenous waste products including ammonia, possibly aromatic amino acids (leucine, isoleucine, valine) and methionine, as well as gamma-aminobutyric acid (GABA) and fatty acids, that can act as toxins. These substances are derived from the gastrointestinal tract, either consumed in the diet or synthesized by the gastrointestinal flora and are normally detoxified in the liver. In animals with portosystemic shunts and/or a significant loss of liver function, these toxins can enter the peripheral circulation and subsequently pass the blood-brain barrier, where they may then alter the central nervous function through a range of different mechanisms including the modulation of neurotransmitters or receptors. Dietary management is the cornerstone in treating dogs with HE.

Clinical Signs of Hepatic Encephalopathy	
Subclinical	Clinical
<ul style="list-style-type: none"> ● Anorexia ● Drowsiness ● Lethargy ● Ptyalism ● Vomiting 	<ul style="list-style-type: none"> ● Personality change <ul style="list-style-type: none"> – Irritable – Aggressive – Dull ● Ataxia ● Weakness ● Disorientation ● Coma ● Seizures

MANAGEMENT

The objectives of therapy are the elimination of causative agents (if known), the reduction of inflammation and minimization of fibrosis, the provision of optimum conditions for hepatic regeneration, and the control of complications such as secondary bacterial infection, ascites, and hepatic encephalopathy.

Dietary management is the cornerstone of the treatment for dogs with liver disease.

Dietary Management

The goals of nutritional therapy are to provide optimal nutrition to meet the patient's requirements for maintenance, to correct any deficits or imbalances, and to provide adequate nutrients for hepatic regeneration and repair.

Dietary management is a very important aspect in the overall management of dogs with liver disease and is aimed at supporting liver function, irrespective of the underlying cause. This involves a number of dietary changes, including the macronutrients protein, fat, and carbohydrate, but also certain minerals, in particular zinc and copper, and vitamins.

Patients with liver disease require a highly digestible and palatable diet, as they may be inappetent.

Maneuvers that may improve the acceptance of a diet include gradual introduction through mixed feeding with the pet's current diet, serving fresh food, warming the food to body temperature, and the feeding of small meals throughout the day. The latter practice will also help reduce the prevalence of fasting hypoglycemia and increase daily protein tolerance, thereby improving the management of hepatic encephalopathy (HE).

Benzodiazepine appetite stimulants should be avoided because they may exacerbate HE. Patients should not be allowed to become constipated, as this will result in increased production and absorption of toxins from the colon.

Energy

It is important to maintain the patient's body weight and correct any previous weight loss with a highly palatable, energy-dense food. The energy requirements of the patient should be individually assessed depending on the animal's body weight and *ideal* body weight, body condition, and activity levels.

In the acute stages of liver disease and in patients with necroinflammatory lesions, the primary nutritional objective should be to prevent weight loss. If in the acute stages the patient is unable to meet its requirements by voluntary food intake, then some form of tube feeding should be considered. During the recovery period, the emphasis should be on restoring body condition. Maintenance of body weight is the goal in patients with chronic liver disease.

It is crucial to provide the patient with good quality protein, but also sufficient nonprotein calories to minimize the use of amino acids for energy (gluconeogenesis) and replace hepatic glycogen stores. A moderate fat level in the diet is advantageous in that it will increase the calorie density of the diet, as well as its palatability, which is particularly important in patients with a poor appetite, as is often seen in animals with liver disease.

Protein

Patients with liver disease may be presented with muscle wasting and abnormal plasma amino acid profiles. This demonstrates the crucial role the liver plays in protein metabolism and highlights the importance of feeding adequate levels of high quality protein to meet the requirements for maintenance *and* hepatic regeneration.

The recommendation is to feed moderate protein levels, with a minimum restriction of 2.1 g/kg/day (10-14% of total calories). A moderate restriction is important in order to balance a sufficient protein intake for hepatic regeneration and repair against minimizing the production of nitrogenous waste products of protein catabolism and the development of hepatic encephalopathy (HE).

Fat

It is recommended to feed a moderate fat level of about 2-3 g/kg/day (30-50% of total calories). A moderate fat level is advantageous in that it will not only increase the calorie density of the diet but also its palatability. This is particularly important as appetite is often variable or reduced. Cholestatic liver diseases may be associated with reduced bile acid production and consequently impaired fat absorption, but steatorrhea and fat malabsorption are usually mild (Thompson 1973). Therefore a further fat restriction is indicated only if there is a true fat intolerance.

Carbohydrates

Carbohydrates are an important source of calories in a diet with moderately restricted protein and fat levels and should be provided at 5-8 g/kg/day (30-50% of total calories). The majority should be provided in form of complex carbohydrates, which prolong the period over which glucose is absorbed and then delivered to the liver, thus reducing glucose intolerance and gluconeogenesis.

The inclusion of soluble fiber reduces the production and absorption of ammonia and thus increases protein tolerance by:

- Increasing nitrogen uptake by intestinal bacteria
- Inhibiting the production of ammonia by colonic bacteria
- Reducing colonic pH through fermentation of the soluble fiber to fatty acids, which increases the formation of NH_4^+ , reducing the availability of easily absorbable NH_3

The inclusion of insoluble fiber decreases the colonic transit time and prevents constipation and therefore the time available for ammonia absorption.

Vitamins

Supplemented levels of water soluble vitamins (B and C) allow for the decreased synthesis, storage and conversion within the impaired liver, and levels of vitamin C supplementation of up to 25 mg/day have been recommended (Strombeck *et al.* 1983). The supplementation with vitamin E at 500 mg/day may provide a protective effect against copper toxicity and lipid peroxidation (Rutgers and Harte 1994).

However, vitamin A supplementation is unwarranted and may even be dangerous, as the combination of vitamin A and cytokines can provoke further hepatocellular damage.

Minerals

Restricting copper intake and absorption in patients with cholestasis or specific copper-storage diseases helps to reduce hepatocellular accumulation and associated cellular injury.

Zinc supplementation aids:

- Against deficiencies due to reduced intestinal absorption, poor dietary intake, or increased urinary losses
- The inhibition of intestinal absorption of copper and alters its storage form in the liver
- The detoxification of ammonia in the urea cycle and reduction of muscle ammonia production
- The inhibition of collagen accumulation and protection against free radical damage against deficiency commonly reported in human patients

A moderate sodium restriction helps to reduce the occurrence of portal hypertension and ascites resulting from sodium retention and hypoalbuminemia.

SUMMARY

Dogs may develop a range of inflammatory and noninflammatory liver diseases, the most commonly being noninfectious inflammatory diseases.

The liver performs many vital functions with respect to nutrient digestion and metabolism, detoxification and excretion, hematology and coagulation, and hormonal balance. Therefore dietary management plays an important role in the overall treatment of dogs with liver disease and is designed to support liver function, irrespective of the type of disease diagnosed. The goals of nutritional therapy are to provide optimal nutrition to meet the patient's requirements for maintenance, to correct any deficits or imbalances, and to provide adequate nutrients for hepatic regeneration and repair. Essentially, canine patients with liver disease require a highly digestible diet which is moderately restricted in protein quantity but not quality, with a high energy density provided by fat and carbohydrate. Additional dietary characteristics include increased levels of water-soluble vitamins and vitamin E, enhanced zinc, and restricted copper and sodium, combined with a moderate level of soluble and insoluble fiber.

Many animals with severe liver disease will be anorectic and may object to the introduction of a new diet. The palatability of the diet is therefore an essential consideration.

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