Copper Toxicity in the Canine Liver

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Introduction

The 19th century American philosopher, William James, once said, "Is life worth living? It all depends on the liver." And he was right. The liver is a vital organ that performs more than 1000 biological functions, the most important of which include: protein synthesis, detoxification, glycogen storage, hormone production, red blood cell decomposition and the production of bile. The liver is a major organ involved in digestion of food and distribution of nutrients (carbohydrates, fats, and proteins) to the cells in the body. Consequently, liver disease can reduce or eliminate one or more of these functions – most of which are critical to life. While there are many disease processes that can affect the liver, this chapter will focus on copper toxicity and its effect on hepatic function. First, we will review how copper is involved in daily biological functions and the dog's dietary needs, and then will discuss the pathophysiology, clinical signs and treatment of copper toxicity.

Copper's Role in the Body

Copper is an important trace mineral that plays a role in a variety of metabolic processes. Its main function is to act as a cofactor for enzymes, meaning that by binding to an enzyme, copper makes it possible for the enzyme to properly carry out its intended biological activities. Below are some of the processes in which copper is a key player:

Energy Production (ATP Synthesis): To understand how copper is involved in the synthesis of energy by cells, it first is important to recognize where energy is produced in the cell and in what form. Cells contain small structures called mitochondria that serve as powerhouses for the cell. The mitochondria contain enzymes that convert specific breakdown products of sugars, fats and proteins into high-energy compounds called ATP. ATP then is used to power a variety of cellular functions. One of the enzymes involved in this process, cytochrome c, is present in one of the membranes that comprise the mitochondria. This enzyme is part of a series of proteins whose function is to pump hydrogen ions across the membrane. When the hydrogen ions flow back across the membrane, they drive a special enzyme that synthesizes ATP. Because copper is a critical component of cytochrome c, acute copper deficiency (usually due to a lack of copper in the diet) decreases the ability of cytochrome c to carry out its function, thereby reducing ATP production. As you might expect, a reduction in ATP would result acutely in fatigue and impaired brain function, and long-standing copper deficiency can be life-threatening. **Figure 6.5** depicts cytochrome c oxidase and its role within the processes that produce energy for cells.

Elimination of Free Radicals: To appreciate the role that copper plays in preventing cellular membrane damage by 'free radicals', it is important to understand what they are and where they arise. During the cell's normal metabolic processes, compounds are derived from oxygen molecules that are used by the cell during the production of energy. These compounds, called either reactive oxygen molecules, peroxide free radicals or free radicals, have the ability to damage cellular membranes. To prevent these potentially damaging effects of the free radicals, cells make an enzyme called superoxide dismutase (SOD) that removes the

Common Clinical Findings
Loss of Appetite
Abdominal Pain and Vomiting
Jaundice
Increased Liver Enzymes in Blood

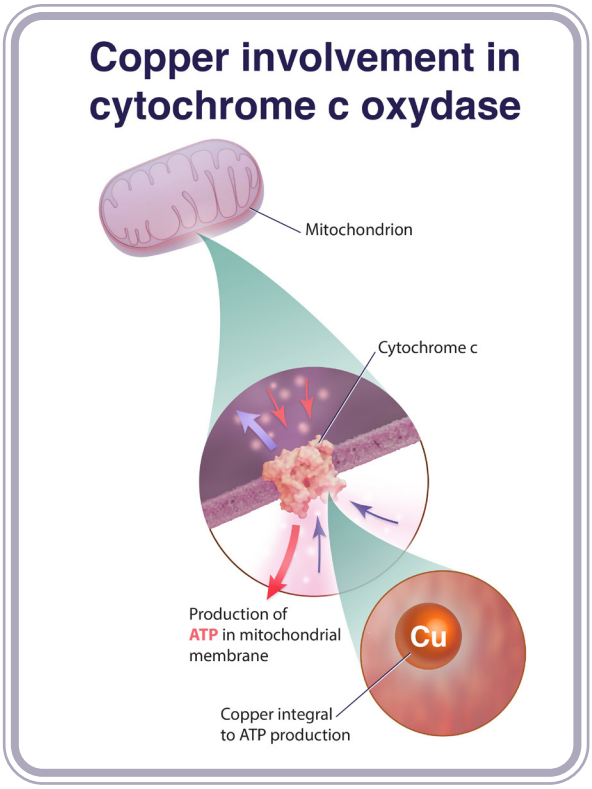

Figure 6.5 - An illustration depicting the central role of copper in the production of ATP by cytochrome c in mitochondria.

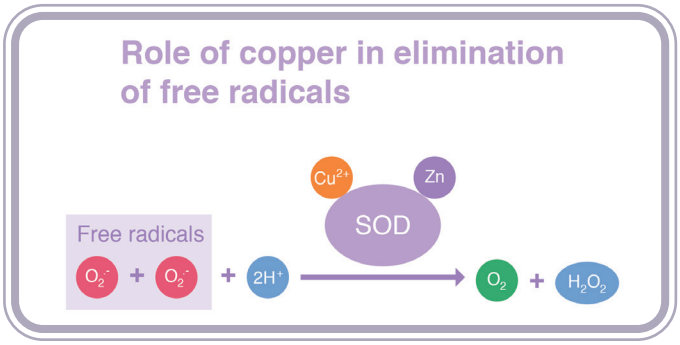

Figure 6.6 - A graphical representation of the elimination of free radicals by the enzyme superoxide dismutase (SOD).

free radicals and turns them into compounds that have no damaging capabilities. This is often referred to as the 'antioxidant' effect of SOD. The enzyme SOD depends on copper being present in order to function as an antioxidant. In fact, copper (along with zinc) serves as a critical cofactor for SOD, allowing it to prevent the effects of the free radicals. **Figure 6.6** depicts how the copper-dependent enzyme SOD functions to prevent oxidative damage in the body.

The Role of Copper in Facilitating the Uptake of Iron

One of the most important chemical elements in the body is iron. For example, iron is a key component of the heme group that allows hemoglobin in the blood to bind and carry oxygen from the lungs to the tissues. Iron also is a component of myoglobin, a protein in skeletal muscle that binds oxygen and makes it available to the muscle cells when needed. Iron also participates in DNA synthesis and cell division, maintaining the immune system, and in the function of neurotransmitters. Copper plays an important role in the uptake of iron by the body, by serving as a component of ceruloplasmin, a transport protein in blood serum, that also functions as an enzyme for catalyzing the oxidation of minerals such as iron. This oxidation process allows iron to bind to its transport protein (transferrin) and to be distributed to tissues in the body. Both copper deficiency and hepatic disease can lead to the same outcome – iron deficiency. Without copper, ceruloplasmin cannot be synthesized by the liver, and without a healthy liver, synthesis of plasma proteins will be decreased.

Copper Plays a Key Role in Pigmentation

Copper is a cofactor for another enzyme called tyrosinase, the enzyme that catalyzes the synthesis of melanin, the primary protective pigment in skin. Tyrosinase in melanocytes converts the amino acid tyrosine to melanin. Consequently, if the tyrosinase enzyme is lacking or nonfunctional, the end result is albinism, an inherited recessive genetic condition. There is a rare genetic disorder in people called Menkes Disease in which copper is poorly distributed to the body's cells; one of the findings in this disease is sparse, kinky hair, although the effects on the nervous system are far more critical.

In summary, copper directly or indirectly controls many important functions in the body. Too little copper may lead to a loss of key activities such as the control of free radical damage, loss of immune functions, and impairment of iron transport and function. However, too much copper is also bad and is described more fully below.

Copper in the Diet

The National Research Council provides recommendations to the pet food nutrient industry about the dog's daily requirements for different elements, including copper. The major dog food companies have spent millions of dollars formulating foods that contain the correct ratios of nutrients for growth, maintenance, or even for dogs suffering from disease. Therefore, if your Westie is fed one of these

commercial diets, it is getting the proper amount of nutrition. With that said, we have read some conflicting reports stating that many dog foods provide excess copper. A quick perusal down the dog food aisle and examination of the nutrition labels was fruitless; the copper content is often not listed. We were also unable to determine the copper content of some commercially available dog foods by searching company websites. If you are interested in how much copper is in your dog food and the information is not provided on the label, do not hesitate to contact the company. They are usually more than happy to provide nutritional information. Dogs that are fed home-made rations run the risk of developing nutrient imbalances and associated disease processes. Some owners who formulate these homemade diets may not properly balance nutrients. It is important to discuss diet and dietary change with your veterinarian, whether you are using a commercial diet or one you make at home.

Dietary sources of copper include fish, some mollusks, cashews, sesame seeds, liver, legumes (beans), raisins (not especially good for dogs), cocoa (definitely a no-no for dogs), olives, and avocados (another no-no). Copper absorption occurs throughout the intestinal tract, but as with most other nutrients, the majority of the absorption occurs in the small intestine. Once absorbed, copper is stored mainly in the liver, with lesser amounts being stored in muscle, kidneys, brain, and heart. Hepatic concentrations of copper reflect an animal's intake and copper status. In healthy dogs, if amounts of copper are excessive, it is normally excreted in the bile.

Copper Toxicity – Pathology and Clinical Signs

Accumulation of toxic levels of copper in the liver is a heritable trait that can be present in many animals, including dogs. The inherited problem is either an inability to properly metabolize copper or the result of a copper storage disease. The end result is the same - chronic liver failure. Most research studies list the Bedlington Terrier as the most susceptible dog breed, but other breeds predisposed to copper toxicity include the West Highland White Terrier, Skye Terrier, Doberman Pinscher, Labrador Retriever, Keeshond, and American Cocker Spaniel (Dodds, 2011). Healthy dogs have a mean copper concentration in the liver of 200-400 ppm on a dry weight basis. In contrast, concentrations exceeding 2000 ppm are considered toxic; dogs with copper toxicosis can have copper concentrations as high as 10,000 ppm.

Dogs with this heritable trait start to accumulate copper early in life and show no clinical signs at first. During this early stage, the copper concentration in the liver can quickly reach a concentration of 1500 ppm, a level bordering on toxicity. If the veterinarian suspects copper toxicosis due to clinical signs of liver failure, it may be advisable to obtain a surgical biopsy of the liver. A histological preparation of biopsied tissue (stained with rhodanine and hematoxylin) would to show copper deposition. **Figures 6.7 and 6.8** show copper granules stained red-brown by the rhodanine stain in the liver from two dogs with copper toxicosis.

In the second stage of the disease, copper levels will continue to increase to values approaching 2000 ppm and there will be obvious microscopic evidence of hepatitis (liver inflammation, scarring and cell loss). Blood work often reveals

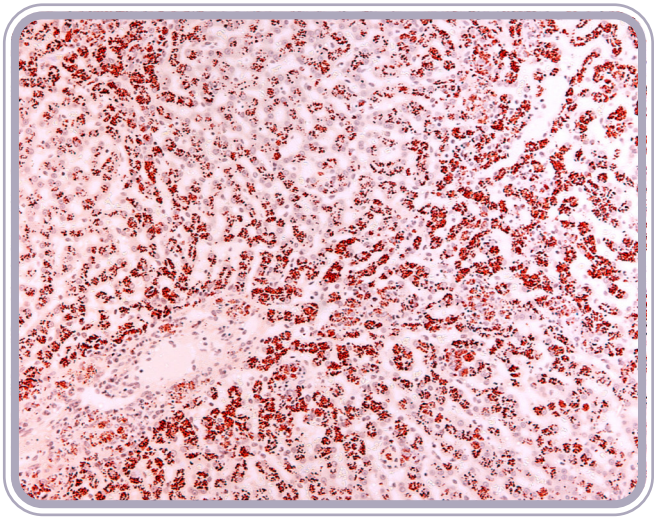

Figure 6.7 - A low power magnification of the liver of a dog with copper toxicity. The red pigmented granules are evidence of copper deposition. (Image courtesy of Dr. Susan Haywood, School of Veterinary Science, University of Liverpool)

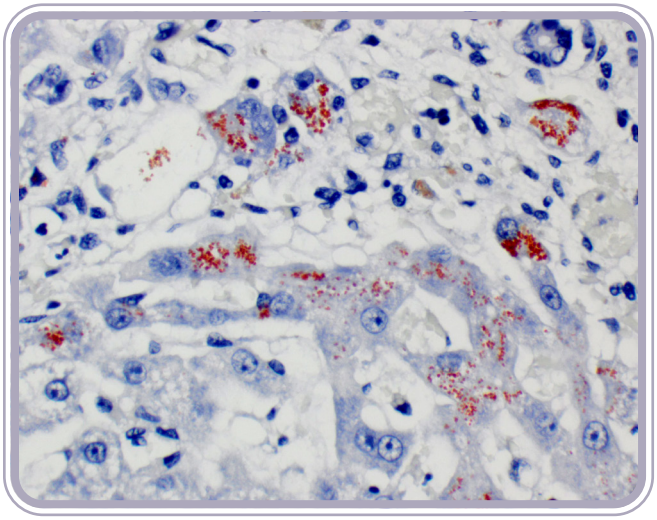

Figure 6.8 - A high power magnification of the liver of a dog with copper toxicity. The red pigmented granules within the cells are evidence of copper deposition. (Image courtesy of Dr. Cathy Brown, College of Veterinary Medicine, University of Georgia)

increased circulating activities to two liver enzymes, alanine aminotransferase (ALT) and alkaline phosphatase (ALKP), as well as alterations in bilirubin, albumin and the number of red blood cells; all of these changes are due to decreased liver function. As copper concentrations exceed 2000 ppm, the liver is no longer able to function and portions become necrotic (dead). An animal at this stage may present with loss of appetite, depression, abdominal pain, vomiting, increased thirst and urination, jaundice, and weight loss. Unfortunately, these clinical signs may be seen with many other diseases as well, so your veterinarian will have to take a thorough history and run some laboratory tests to properly diagnose copper toxicosis. As noted above, it may be necessary to do a surgical biopsy of the liver to make a definitive diagnosis of copper toxicity.

Treatment Options

The goals of treatment for copper toxicity in dogs are:

- To reduce further absorption of copper from the gastrointestinal tract
- To promote copper excretion
- To preserve liver function and encourage liver healing

This can be achieved by feeding a diet low in copper, combined with supplements and medications that reduce copper absorption and enhance its secretion (Filippich, 2009). The first step is a dietary change. Your veterinarian will either prescribe or help you formulate a diet that is low in copper. Do not do this yourself as it can lead to other nutrient deficiencies/toxicities!

Simultaneously, the veterinarian may decide to decrease intestinal absorption of copper by the oral administration of zinc, an element that competes with copper and similar elements in the diet. The daily dosage of zinc must be controlled very closely as providing excessive amounts of zinc can cause serious gastrointestinal upset and hemolytic anemia if zinc toxicosis occurs. Your veterinarian will prescribe an appropriate zinc supplement for you to use.

In addition to changes in the diet and supplementation with minerals, your veterinarian may also prescribe a chelating drug, such as d-penicillamine, a substance that forms complex molecules with certain metal ions, thereby inactivating the ions so that they cannot react detrimentally with other chemicals to produce precipitates. Once the chelating drug binds to copper, the complex that is formed can be excreted in the urine. Dogs being treated for copper toxicosis should be examined on a regular basis by the veterinarian. These examinations will include performing the appropriate blood work, to be sure that hepatic function is returning to normal and that there are no adverse reactions to the medications.

The liver, as an organ, has a lot of 'reserve capacity" and the ability to heal by regeneration of tissue. In response to a reasonable amount of damage, cells may be quickly replaced (within hours to days). However, if there is a lot of damage to the blood supply or bile channels, and/or a lot of scar formation, healing does not proceed well. Chronic copper toxicity is a disease that can cause a lot of liver scarring and severely affected dogs are unlikely to regain normal liver function. These dogs may have continued problems with digestion, maintaining body condition, susceptibility to infections and decreased immunity. Because the liver synthesizes blood clotting proteins, some affected dogs may develop clotting abnormalities. It is very important to get an accurate diagnosis of copper toxicity in early stages of the disease to prevent significant (and often permanent) liver damage.

One final note: It is currently thought that most cases of copper toxicity are due to inherited defects in copper metabolism. Affected dogs should not be bred so that this defect is not passed to future generations.

Current Research About Copper Toxicity in the Canine Liver

Mutton J, Yeomans S, White J. Copper hepatopathies in Australian dogs. Aust Vet J 2024 Aug;102(8):385-391.

This study was performed to describe the prevalence and survival of dogs with copper-associated hepatopathy. Medical records were reviewed to identify dogs with liver disease and liver biopsy between November 2008 and November 2021. Copper-associated hepatopathy was defined as (i) histological evidence of copper accumulation in centrilobular areas associated with hepatocyte necrosis, inflammation with copper-laden macrophages and chronic hepatitis (ii) histochemical copper staining showing hepatocyte copper accumulation in the centrilobular areas and iii) increased hepatic copper concentrations in samples of the liver. Sixty-seven dogs were included. Copper-associated hepatopathy was common among Australian dogs with chronic hepatopathies, occurring in younger and heavier dogs than other causes of primary inflammatory parenchymal liver disease. Clinical pathology is not useful for differentiating between copper-associated hepatopathy and other causes of chronic primary inflammatory parenchymal liver disease. When copper-associated hepatopathy is treated, the prognosis can be good.

Amundson LA, Kirn BN, Swensson EJ et al. Copper metabolism and its implications for canine nutrition. Transl Anim Sci 2024 Jan 3:8147.

Canine copper nutrition has received increased attention due to recent reports of apparent copper-associated hepatitis. Recent trends in consumer preference for dog diets, supplements, and treats introduce a layer of complexity, as most ingredients used in these formulations provide vastly different proportions of essential nutrients, thus resulting in great variation in nutrient profiles available to the animal. Copper metabolism and status in animals is affected by a multitude of factors including absorption, storage, excretion, and nutrient interactions. Given its vital role in many physiological processes, it is important that both nutritional deficiencies and toxicities be avoided. Additionally, another challenge for proper copper nutrition in dogs is the known genetic predispositions of some breeds for copper storage and excretion abnormalities. Therefore, it is imperative that veterinarians, nutritionists, and pet food manufacturers collaborate with the shared goal of providing dog food options that supply the essential nutrients at adequate concentrations to support an active and healthy life. Future research should focus on discovering reliable, non-invasive methods for evaluating canine copper status, a deeper understanding of genetic predispositions of certain breeds, increased knowledge of copper contributions from various ingredients, and the role of physiological stressors on copper metabolism.

Haywood S, Swinburne J, Schofield E, et al. Copper toxicosis in Bedlington terriers is associated with multiple independent genetic variants. Vet Rec 2023;193(4):e2832.

Bedlington terrier copper toxicosis is due to a homozygous exon deletion in COMMD1. Copper toxicosis also occurs in Bedlingtons lacking this deletion. An association with two ABCA12 single nuceotide polymorphism splice variants was reported. Labrador retriever copper toxicosis is associated with a missense mutation in ATP7B, and with a protective mutation in ATP7A. Liver and DNA samples from 24 affected and 10 unaffected Bedlingtons were assessed for copper and genetic variants. Allelic frequencies were compared. The ATP7B mutation frequency was investigated in 144 dogs of other breeds. The COMMD1 deletion remains present in Bedlington terriers but is no longer the primary cause of copper toxicosis. The ATP7B:c.4358G>A mutation was significantly associated with Bedlington copper toxicosis and was more common in dogs of this breed than in the 144 dogs of other breeds.

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