**CANINE HYPERLIPIDEMIA**

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**INTRODUCTION**

Hyperlipidemia refers to an increased cloudiness in serum due to an excess of circulating lipids. Serum hyperlipidemia is normal after ingestion of a meal, but is abnormal in an animal fasted for 12 hours or more. Perturbations in any aspect of lipid metabolism may result in abnormal hyperlipidemia. Abnormalities may occur in lipid absorption, synthesis, esterification, lipoprotein synthesis, receptor-mediated uptake, bile formation and circulation, or reverse cholesterol transport.

**LIPOPROTEIN PRODUCTION**

Lipoproteins are the main carriers of cholesterol in the blood and are important in the delivery of cholesterol to all tissues. Circulating lipoproteins are classified by their size, density, and electrophoretic behavior. Lipoproteins in humans have been well characterized, but direct correlations cannot be made to the canine due to many differences in lipoprotein characteristics.

Five major classes of lipoproteins have been characterized, including chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). Mammals with a predominance of LDL are classified as "LDL mammals" and include humans, rabbits, hamsters, guinea pigs, pigs, camels, rhinoceros, and most monkeys. LDL mammals are more sensitive to elevations in LDL cholesterol and the development of atherosclerosis. Mammals with a predominance of HDL (HDL mammals) include dogs, cats, horses, ruminants, rats, mice, and most other mammals. HDL mammals are less sensitive to elevated LDL cholesterol concentrations, and are more resistant to the development of atherosclerosis.

In general, the larger lipoproteins are less dense, contain less protein, and more lipid. Chylomicrons are the largest of the lipoproteins with the lowest density. In the peripheral circulation, lipoprotein lipase hydrolyzes triglyceride in chylomicrons creating chylomicron remnants which are rapidly removed by the liver. VLDL are synthesized by hepatocytes and are a major transporter of triglyceride. Lipoprotein lipase hydrolyzes triglyceride in VLDL creating a VLDL remnant which can also be removed by the liver. With further loss of triglyceride, LDL is formed, and is removed from the circulation via an hepatic receptor.

HDL is secreted by the liver, and contains very little free cholesterol and cholesteryl ester. Free cholesterol is transferred from peripheral cells to HDL, and these cholesterol-rich particles serve as substrate for lecithin:cholesterol acyltransferase (LCAT), converting free cholesterol to cholesteryl esters. Hepatic lipase may also play a role in the interconversion of HDL subfractions. The conversion of free cholesterol to cholesteryl esters and its subsequent transfer to other lipoproteins allows additional free cholesterol to transfer from the surface of cells and other lipoproteins to HDL. Thus LCAT plays a key role in the transfer of free cholesterol from peripheral tissues to the liver.

**DIAGNOSTIC APPROACH TO THE HYPERLIPIDEMIC PATIENT**

If a patient exhibits serum hyperlipidemia after a 12 hour fast, investigation into the cause of the hyperlipidemia is warranted. The presumption that the dog was fasted should be verified, and once fasting has been confirmed, causes of secondary hyperlipidemias should be investigated. If no secondary disorder resulting in hyperlipidemia can be identified, then a primary lipid abnormality should be considered.

Serum turbidity can help provide an estimation of the serum triglyceride concentration. Normal clear serum has a triglyceride concentration of less than 200 mg/dL (2.3 mmol/L), and opacity is seen when the triglyceride concentration reaches 600 mg/dL (6.8 mmol/L). Serum with the appearance of whole milk may have a triglyceride concentration greater than 2500 mg/dL (28.3 mmol/L).

A simple refrigeration test may help to identify what lipoproteins are present in the hyperlipidemic sample. The serum sample is placed in the refrigerator, and left undisturbed overnight. Since chylomicrons are the least dense of the lipoproteins, if present, they will float to the top of the serum sample forming a ‘cream layer.’ If the serum below the chylomicron layer is clear, then only chylomicrons are present in excess. If the serum below the chylomicron layer is turbid, then other lipoproteins are also present in excess. If a ‘cream layer’ does not form, then chylomicrons are not present in excess, and the visible hyperlipidemia is due to an excess of one or more other lipoprotein classes. Lipoprotein electrophoresis can be used to characterize the serum lipoproteins present, but unfortunately this technique is not widely available.

**CAUSES OF HYPERLIPIDEMIA**

Fasting hyperlipidemia may be the result of lipid abnormalities secondary to a number of other conditions. Conditions resulting in secondary hyperlipidemia include hypothyroidism, pancreatitis, cholestasis, hyperadrenocorticism, diabetes mellitus, and nephrotic syndrome. These conditions should be investigated and eliminated as potential causes of the hyperlipidemia before primary hyperlipidemia is considered. Elevations of both cholesterol and triglycerides are noted in secondary hyperlipidemias, and an increase in VLDL is a fairly consistent finding. A decrease in lipoprotein lipase activity has been observed in pancreatitis, diabetes mellitus, nephrotic syndrome, and hyperadrenocorticism. With appropriate therapy of the underlying condition, the lipoprotein abnormalities typically resolve.

**PRIMARY HYPERLIPIDEMIA**

When all causes of secondary hyperlipidemia have been ruled out, a presumptive diagnosis of primary hyperlipidemia is made. In the dog, several different types of primary hyperlipidemia have been observed, including idiopathic hypercholesterolemia, idiopathic hypercholesterolemia, and idiopathic hyperlipoproteinemia. Etiologies of these conditions have not been established, and it is likely that a number of different primary syndromes with differences in etiology will be identified in dogs as in humans.

**Idiopathic Hypercholesterolemia.** Idiopathic hypercholesterolemia has been reported in Briards, and has also been observed in several other breeds, including a miniature bull terrier, and Shetland sheepdogs. These dogs have unexplained fasting hypercholesterolemia, with normal
concentrations of serum triglycerides. Serum is not hyperlipidemic since triglycerides are not elevated. An increase in HDL has been noted in dogs with idiopathic hypercholesterolemia.

Idiopathic or Primary Hyperlipoproteinemia. Primary hyperlipoproteinemia has been observed in a number of dog breeds including the miniature schnauzer, Shetland sheepdog, beagle, miniature poodle, cocker spaniel, English cocker spaniel, and mixed-breed dog. Miniature schnauzers appear to have a higher incidence of primary hyperlipoproteinemia, however any breed of dog may be affected. Clinical signs associated with primary hyperlipoproteinemia may include abdominal pain (presumptively due to pancreatitis) and seizures, but many dogs exhibit no obvious clinical signs.

Dogs with primary hyperlipoproteinemia have moderately increased serum cholesterol concentrations, and moderate to marked increases in serum triglyceride concentrations. There are consistent increases in VLDL and LDL, and chylomicrons and HDL; may be normal or increased.

In ten clinically healthy dogs of various breeds diagnosed with primary hyperlipoproteinemia, lipoprotein lipase activity was significantly reduced, and hepatic lipase activity was significantly increased compared to a group of healthy, non-hyperlipidemic control dogs. This study presents the first potential etiology for ‘idiopathic’ hyperlipoproteinemia. Decreased activity of lipoprotein lipase leads to decreased clearance of VLDL and chylomicrons, and hepatic lipase may be increased in a compensatory role.

EFFECTS OF CHRONIC HYPERLIPIDEMIA

The long-term effects of chronic hyperlipidemia in dogs are unknown. Dogs are resistant to the development of atherosclerosis as compared to humans, due to differences in lipoprotein metabolism between the species. For atherosclerosis to develop in the dog, serum cholesterol concentrations greater than 750 mg/dL must be maintained for more than 6 months.

An association of atherosclerosis and hypothyroidism in dogs was noted over 30 years ago, and atherosclerosis has also been associated with diabetes mellitus. Dogs with atherosclerosis are 53 times more likely to have diabetes mellitus, and 51 times more likely to have hypothyroidism compared to dogs without atherosclerosis. An increased incidence of hyperadrenocorticism has not been noted in dogs with atherosclerosis.

The effects of persistent hyperlipidemia in dogs on other organ systems have not been studied. Persistent hyperlipidemia may contribute to progressive renal injury, and may result in an increased incidence of pancreatitis. Chronic hyperlipidemia may also cause diabetes mellitus due to insulin resistance.

TREATMENT OF HYPERLIPIDEMIA

Treatment of the underlying cause of secondary hyperlipidemia usually results in the resolution of hyperlipidemia. However, there is no specific therapeutic regimen for dogs with idiopathic hyperlipidemia. Initial treatment of primary hyperlipidemia involves a switch to a low-fat diet with moderate protein content. Low-protein diets are not recommended as they may result in an increased serum cholesterol concentration. It is important to evaluate the quantity of the fat in the diet based on metabolizable energy (ME), rather than the absolute percentage of fat as stated on the label. Some diets may appear quite low in fat on a percentage basis, but when other ingredients and the metabolizable energy is taken into account, they may not be the lowest fat diets available. For example, a diet containing 10% fat with an ME of 4000 kcal/kg provides only 25 g fat/1000 kcal, whereas a diet containing 8% fat with an ME of 2700 kcal/kg provides 30 g fat/1000 kcal. The presence of a blend of fructooligosaccharides and beet pulp in the diet may also be desirable, since this blend can decrease serum triglyceride and cholesterol concentrations in the dog.

After feeding a low-fat diet for approximately 8 weeks, the presence of fasting hyperlipidemia, serum triglyceride and serum cholesterol concentrations should be re-evaluated. If fasting hyperlipidemia is still present at that time, then fish oil at a dose of 1g/10 lb (1g/4.55 kg) body weight (BW) once daily should be added to the regimen of therapy. Fish oil capsules may be obtained over-the-counter, but labels should be read carefully to ensure that the dog receives 1g/10 lb BW of a combination of the long chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Some products may contain high levels of other fatty acids, and be less desirable. In my experience, the only side effect noted with this level of fish oil supplementation is that the dog may have a noticeable ‘fishy’ odor which may be objectionable to some owners. After the addition of fish oil therapy, the presence of fasting hyperlipidemia, serum triglyceride and serum cholesterol concentrations should be re-evaluated after 6 to 8 weeks. If hyperlipidemia has resolved, and the owner complains of the ‘fishy’ smell, the dosage of fish oil supplementation may be cut in half. A few dogs can be managed at this dose; however, most will require more than this half-dose.

The use of fish oils in the treatment of hyperlipidemia has been studied in a number of species. Human patients taking an EPA supplement showed an average 31% decrease in serum triglyceride concentration. Triglyceride lowering benefits have also been observed in rats, chicks, and rabbits. Fish oils may exert a beneficial effect on hyperlipidemia by stimulating lipoprotein lipase activity, decreasing the intestinal absorption of glucose and lipid, increasing cholesterol secretion into bile, and by decreasing cholesterol absorption. Fish oils also decrease serum concentration of free fatty acids which may be important in the prevention of pancreatitis and diabetes mellitus.

Unfortunately there are no long-term studies to verify the safety and efficacy of any lipid-lowering agent in dogs, and any therapy should be used with caution. One concern with fish oil therapy is that fish oils may increase the concentration of lipoperoxides in LDL. The addition of vitamin E to the fish oil therapy regimen may enhance the beneficial results by decreasing peroxide levels.

Treatments other than fish oil have been attempted with variable results. Gemfibrozil or niacin therapy has been used in a few dogs; however, adverse effects have been noted in both dogs and humans. Thyroxine has lipid-lowering properties, but its use in non-hypothyroid dogs with primary lipid abnormalities has not been investigated. Medium chain triglycerides (MCT) lower serum triglycerides and increase lipoprotein lipase activity, and may be of benefit. However, MCT oil does not lower, and may even elevate serum cholesterol concentrations. Unfortunately, MCT oil is not very palatable which limits its use.
REFERENCES


