Hyperlipidemia Disorders in Dogs

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ABSTRACT:

Lipid disorders are common in dogs, with most arising from secondary causes such as endocrine imbalances, cholestatic liver disease, or protein-losing nephropathies. Two primary lipid disorders—idiopathic hyperlipidemia in miniature schnauzers and hypercholesterolemia in briards—are also recognized. Visualization of a lipemic fasted blood sample or elevated plasma cholesterol or triglyceride in combination with clinical assessment is the method by which most lipid disorders are diagnosed. Cholesterol and triglyceride are components of larger molecules called *lipoproteins*, which have a complex and highly regulated metabolism that is important to understand when altered by lipid disorders.

L ipid disorders are relatively common in veterinary medicine, particularly in dogs. The presence of a lipid disorder provides clues regarding underlying disease and presents a risk factor for other problems. In dogs, lipid disorders are either primary or secondary, of which the latter is by far the most common.[1–4] Primary disorders are considered hereditary in some breeds of dogs.[1,3–6] Secondary disorders can be dietary related or more often of endocrine origin, resulting from an imbalance of homeostatic mechanisms that normally regulate plasma lipids[1–4] (see box on p. 362). Unfortunately, it is not always easy to separate these two based on clinical assessment or biochemical analysis. Therefore, it is imperative that signalment, clinical presentation, and biochemical information for each animal be analyzed collectively when suspecting one of these disorders. This article discusses basic concepts of lipid metabolism, addresses laboratory evaluation of plasma lipids, and examines the causes of hyperlipidemia disorders in dogs.

LIPID METABOLISM

Cholesterol and triglyceride are clinically relevant plasma lipids (Figures 1 and 2). Free cholesterol and triglyceride are water insoluble in plasma, so they are transported via water-soluble lipoproteins in plasma. There are four general types of lipoproteins: chylomicrons, very–low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Intermediate-density lipoprotein is also recognized but is considered less important. Humans have two HDL molecules: HDL_2 and HDL_3. Dogs have HDL_2 and HDL_3 but are unique in that they have HDL_1, which is recognized by a distinct α_2 band on lipoprotein electrophoresis.[1,3,7]

Lipoproteins exist in plasma as spherical structures composed of an outer shell and an inner core (Figure 1). The outer shell has both hydrophilic and hydrophobic properties containing free cholesterol, apoproteins, and phospholipids.[3,7] Apoproteins serve as cofactors for cholesterol-shuttling enzymes, receptors for uptake and delivery of tissue cholesterol and triglyceride, and receptors for removal of remnant lipoproteins by the liver. The inner core consists of hydrophobic lipids, primarily cholesterol esters and triglyceride.[3,7]

Chylomicrons are created by intestinal epithelial cells following fatty meal ingestion.
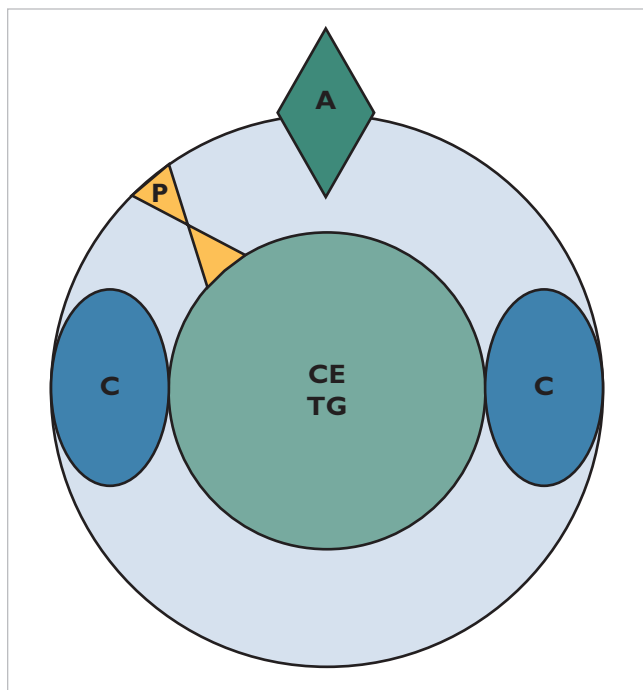
Figure 1. Basic lipoprotein structure. (*A* = apoprotein; *C* = cholesterol; *CE* = cholesterol ester; *P* = phospholipid; *TG* = triglyceride)

They are large molecules composed primarily of triglyceride with smaller amounts of cholesterol. Chylomicrons transport triglyceride to tissue, such as muscle or fat. A critical enzyme called *lipoprotein lipase*, which is located on the endothelium in many tissues, mediates this transport.[3,7,8] Lipoprotein lipase hydrolyzes triglyc-

Causes of Primary and Secondary Lipid Disorders in Dogs

Primary
- Idiopathic hyperlipidemia in miniature schnauzers
- Hypercholesterolemia in briards

Secondary
- High-fat diets
- Diabetes mellitus
- Hyperadrenocorticism
- Hypothyroidism
- Acute pancreatitis
- Protein-losing nephropathy
- Cholestasis

may be removed from circulation by the liver or may undergo further triglyceride depletion by lipoprotein lipase or a second enzyme called *hepatic triglyceride lipase*, forming smaller and denser LDL.[3,7]

There are notable differences in how dogs and humans process LDL and form HDL. LDL, the "bad lipoprotein," primarily transports cholesterol with smaller amounts of triglyceride for delivery to tissues. Subsequently, remnant LDL particles can be removed from circulation by the liver in both species, similar to remnant VLDL. In humans, a process called *cholesterol shuttling*, which is mediated by cholesterol ester transfer protein, enables triglyceride to be transported directly from LDL or VLDL to HDL_3 in plasma in exchange for cholesterol esters, consequently forming cholesterol ester–rich LDL and triglyceride-rich HDL_2, respec-

Understanding basic lipoprotein metabolism is important because many diseases alter this process, leading to elevated plasma lipid levels.

eride within chylomicrons to long-chain fatty acids and glycerol for active uptake by cells.[8] Insulin and thyroxine are known to enhance the activity of this enzyme.[8] After triglyceride is delivered to tissue, remnant chylomicron particles are removed from circulation by the liver.

VLDL is produced by hepatocytes and is smaller than chylomicrons but also contains similar cholesterol and triglyceride proportions. Lipoprotein lipase also hydrolyzes triglyceride within VLDL, subsequently forming remnant VLDL. Remnant VLDL particles

tively.[3,7] Cholesterol ester–rich LDL is removed from the bloodstream by the liver but can also be actively removed from circulation by macrophages lining large arteries, potentially leading to atherosclerosis. Unlike humans, dogs have no documented activity of cholesterol ester transfer protein, which likely contributes to their general resistance to this detrimental phenomenon.[3,7,9]

Native HDL, the "good lipoprotein," is produced by the liver and transports cholesterol from tissue back to the liver (i.e., the so-called "reverse cholesterol trans-
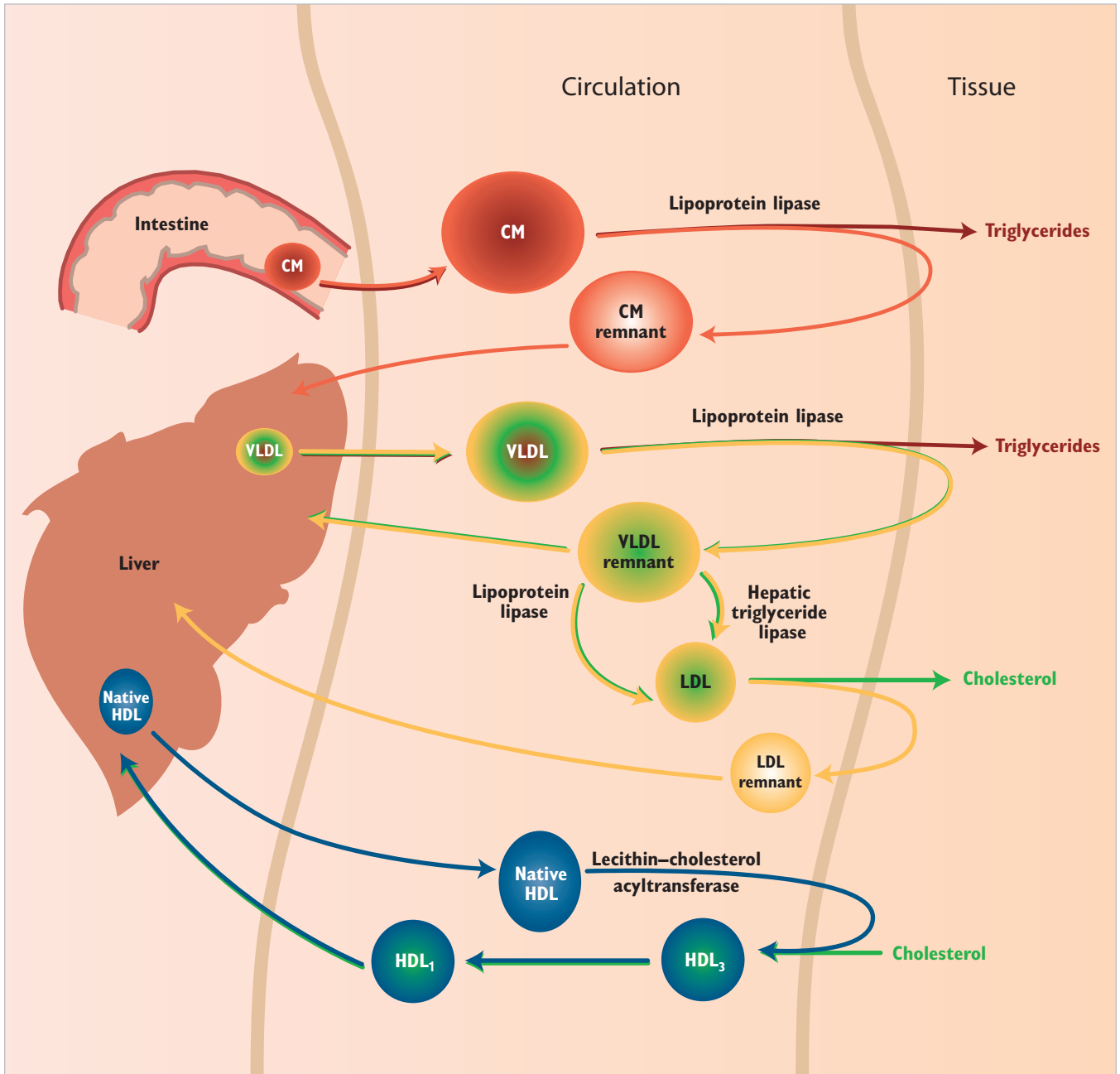
Figure 2. Canine lipoprotein metabolism. Cholesterol and triglycerides are transported in plasma via four lipoproteins: chylomicrons (CMs), VLDL, LDL, and HDL. CMs are made in the intestine. Lipoprotein lipase releases triglycerides into the tissue. Remnant CMs are removed from circulation by the liver. VLDL is made by the liver. Lipoprotein lipase releases triglycerides into the tissue. Remnant VLDL is removed by the liver or degraded by the enzymes lipoprotein lipase or hepatic triglyceride to LDL, which transports cholesterol to the tissue. Remnant LDL is removed by the liver. Native HDL is made by the liver and transports tissue cholesterol to the liver with the help of lecithin–cholesterol acyltransferase. Native HDL then becomes HDL$_3$, which incorporates additional cholesterol esters and becomes HDL$_1$, which is removed from the blood by the liver.

port" mechanism). Lecithin-cholesterol acyltransferase (LCAT), which is an enzyme bound to native HDL in circulation, converts free cholesterol from tissue to cho-lesterol esters for incorporation into HDL molecules.[3,7] These cholesterol ester–rich molecules are called *HDL₃* in both species. Because dogs do not have cholesterol

ester transfer protein activity, most HDL_3 continues to acquire cholesterol esters and results in formation of the unique HDL_1 molecule. Consequently, HDL_1 is usually increased with hypercholesterolemia in dogs.[3,7] Cholesterol ester–rich HDL can be removed from the blood by receptor-mediated endocytosis in the liver for possible reuse. Recent evidence in cultured mouse adrenal cells also shows that cholesterol esters can be removed from cholesterol ester–rich HDL by scavenger receptors (class B, type 1) without endocytosis of the HDL molecule.[10] This receptor has been characterized in humans, but a canine counterpart has not been identified in the literature.[11]

LABORATORY FEATURES OF LIPID DISORDERS

Increased plasma lipids are often discovered in dogs only serendipitously following biochemical testing for a clinically suspected disease that is subsequently known to elicit increased plasma lipids. However, dogs may not exhibit overt clinical signs of such a disease, and laboratory testing may be the only route by which lipid disorders are initially identified. Therefore, routine health screening blood work can be important in early detection of lipid disorders. Dogs should be fasted for 12 hours before blood samples are collected in clot or heparinized glass tubes.[1,12,13]

When plasma levels of either cholesterol or triglyceride are increased, an assumption is made that one or more of the lipoproteins carrying these lipids are also increased. Clinically speaking, however, abnormalities in laboratory data are typically defined by alterations in cholesterol or triglyceride and not in lipoproteins. An increase in plasma lipid is called *hyperlipidemia* and results from increased triglyceride, cholesterol, or both.[13] Hyperlipoproteinemia is often used synonymously with hyperlipidemia but is best used when plasma lipoprotein analysis is actually conducted.[13]

One of the first indications of hyperlipidemia is observation of turbid (i.e., cloudy) or lactescent (i.e., white) plasma, which suggests that lipemia and a lipid disorder may be present.[1,12,13] From a laboratory perspective, lipemia can interfere with certain biochemical tests that use endpoint or kinetic assays and can falsely increase tests using refractometry or spectrophotometry, such as plasma protein and hemoglobin testing, respectively.[14] Spurious biochemical results reported in patients with lipemia are increased total bilirubin, total protein, albumin, globulin, glucose, calcium, phosphorus and bile acid levels.[3,14] Falsely decreased assays can be seen with electrolyte levels and serum activity of amylase, lipase, alanine aminotransferase, aspartate transaminase, and alkaline phosphatase.[3,14]

Lipemia is always associated with elevated plasma triglycerides. However, hyperlipidemia does not always induce lipemia because hypercholesterolemia by itself does not cause lipemia.[13] Consumption of fatty diets can induce transient lipemia for up to 12 hours after eating.[1,3,15] Therefore, it is vital to differentiate chylomicron-induced, postprandial lipemia from VLDL-generated hypertriglyceridemia because the former is usually short-lived and does not typically indicate the presence of a lipid disorder. These disorders can often be differentiated by placing lipemic samples in a refrigerator (i.e., a chylomicron or refrigeration test) for 12 hours. Chylomicrons are larger and less dense than VLDL and tend to form a "cream" layer on top of plasma when refrigerated.[1,13] VLDL often remains suspended in plasma following refrigeration.[1,13] When both chylomicrons and VLDL are present, the sample is turbid with a creamy layer.[1,13]

Lipid biochemical analysis is often needed to identify a potential lipid disorder. In human medicine, detailed lipoprotein analysis is conducted by ultracentrifugation and electrophoresis of plasma. Although many veterinary diagnostic laboratories can conduct this evaluation, this type of testing for veterinary patients is often impractical. Most veterinary chemistry analyzers can quantify plasma cholesterol and triglyceride, which is an indirect reflection of plasma lipoprotein. Serum cholesterol is a usual component of canine chemistry panels, so more attention is initially focused on increased choles-

Cholesterol and triglyceride measurements in plasma are an indirect reflection of plasma lipoprotein content and provide an assessment of their homeostasis in a disease state.

terol values when suspecting a lipid disorder. Triglyceride measurement is not standard to every canine chemistry panel but can be requested as an additional test.

In general, plasma cholesterol exceeding 300 mg/dl is considered increased.[1,13] The magnitude of cholesterol increase may reflect the seriousness of the clinical disorder, especially with extreme elevations. Cholesterol values of 300 to 500 mg/dl are considered mildly increased, values of 500 to 750 mg/dl moderately increased, and those over 750 mg/dl severely increased.[1] Hypertriglyceridemia follows similar trends used for clinical

> ### *Lipemia in a fasted blood sample indicates the presence of a lipid disorder; however, the absence of lipemia does not exclude this possibility, especially when only hypercholesterolemia is present.*

assessment. Values of 150 to 400 mg/dl are generally considered mildly elevated, results of 400 to 1,000 mg/dl moderately elevated, and those greater than 1,000 mg/dl seriously elevated.[1] Plasma turbidity is often grossly visible with triglyceride values above 300 mg/dl and lactescent with values greater than 1,000 mg/dl.[3]

CLINICAL SIGNIFICANCE OF HYPERLIPIDEMIA

The consequences of persistent hyperlipidemia can be clinically relevant in dogs. Plasma cholesterol values greater than 750 mg/dl predispose dogs to atherosclerosis despite their natural resistance.[1,7] A recent citation reported that dogs with atherosclerosis are 53 times more likely to have diabetes mellitus (DM) and 51 times more likely to have hypothyroidism, both of which are known secondary causes of hyperlipidemia.[16] Xanthomas (i.e., yellowish raised skin nodules or plaques composed of foamy macrophages laden with lipid) are often seen in cats with hyperlipidemia but are rarely present with hyperlipidemia in dogs.[15,17,18] Although a cause-and-effect relationship between hypertriglyceridemia and pancreatitis and DM has not been established in dogs, a direct correlation between them has been suggested. In humans, elevated plasma lipids associated with type 2 DM have been linked with pancreatic β-cell toxicity and decreased function likely due to accumulation of lipid metabolites in these cells.[19] Hypertriglyceridemia can be associated with abdominal pain, vomiting and diarrhea, lipemia retinalis and clouding of the aqueous humor, lethargy, hepatomegaly, and seizures.[1,12,15]

PRIMARY LIPID DISORDERS

Primary lipid disorders are rare in dogs, and the mechanisms inducing them are often unknown. Idiopathic hyperlipidemia in miniature schnauzers and hypercholesterolemia in briards are the two recognized primary lipid disorders in dogs, although references also describe familial hyper-

lipoproteinemia in beagles, hypertriglyceridemia in two related Brittanys, and congenital lipoprotein lipase deficiency in a mixed-breed puppy.[1,3,5,6,20–23]

Idiopathic hyperlipidemia in miniature schnauzers is by far the most common primary disorder. Although this complex metabolic syndrome is considered to have familial tendencies, no defined genetic defect has been characterized. Lipemia and thus hypertriglyceridemia are commonly reported; hypercholesterolemia is also documented but is less consistent.[1,5] Lipoprotein evaluations in one study revealed increased VLDL with variable chylomicron results.[5] Miniature schnauzers may have concurrent acute pancreatitis. This poses the question of which came first—pancreatitis or hyperlipidemia—because acute pancreatitis is a common secondary cause of hyperlipidemia.[1,3–5] Although not proved, it is conceivable that patients with idiopathic hyperlipidemia may have an increased risk of developing DM, especially if they have concurrent acute pancreatitis.[5] Some of the clinical features documented with idiopathic hyperlipidemia are abdominal pain, seizures, and vomiting.[5,15,20]

Hypercholesterolemia in briards has been reported primarily in the United Kingdom.[6] It was initially discovered because of an association with retinal pigment epithelial dystrophy (also called *briard lipid retinopathy*), which is a degenerative disorder affecting the retina. A genetic defect for hypercholesterolemia has not been defined in the literature. This condition is characterized by deposition of lipid droplets within the cells of the retinal-pigmented epithelium. Further studies of the disorder noted that briards had significantly higher plasma cholesterol than did control dogs.[24] Hypertriglyceridemia is not a documented feature of this disorder.

SECONDARY LIPID DISORDERS

Frequent causes of secondary lipid disorders include high-fat diets, DM, hyperadrenocorticism, hypothyroidism, acute pancreatitis, protein-losing nephropathy (PLN), and cholestatic liver disease. Other reports describing hyperlipidemia include glycogen storage disease type 1a in a crossbreed colony of Maltese and beagles with a defective glucose-6-phosphatase gene, dogs with dilated cardiomyopathy, and dogs with chronic *Leishmania infantum* infections.[25–27]

As stated previously, high-fat diets can induce hyperlipidemia that is often transient and causes lipemia 6 to 12 hours after ingestion.[1,15] However, if these diets induce more persistent hyperlipidemia, dogs may be at risk for some of the clinical problems described previously.[15] Interestingly, unlike in humans, cholesterol-enriched diets have not been shown to elevate LDL cholesterol in normal dogs.[28] This is thought to be due to the ability of the canine body to switch classes of VLDL-associated apoprotein made in the liver from apo B_{100} to apo B_{48}, which is normally found in chylomicrons produced by intestinal epithelial cells.[28] This switch enhances VLDL uptake and clearance from the circulation by the liver so that less VLDL is available for subsequent LDL generation.[28]

Hyperlipidemia is reported in both insulin-dependent (type 1) and non–insulin-dependent DM (type 2) in humans. Dogs almost exclusively have type 1 DM.[1–4,29,30] Lack of insulin or insulin resistance causes hyperlipidemia because of impaired insulin interaction with lipoprotein lipase.[13,29] Studies show insulin increases lipoprotein lipase activity levels in human adipocytes without changing transcription of the gene or increasing lipoprotein lipase mRNA levels, suggesting that insulin has posttranscriptional or posttranslational control of lipoprotein lipase.[31] Other mechanisms are also possible, such as increased VLDL production after tissue mobilization of fat to the liver.[29,30] Diabetic dogs often have hypertriglyceridemia and sometimes hypercholesterolemia, which if present may not be as notable as hypertriglyceridemia.[15]

Hyperadrenocorticism, whether primary or from iatrogenic corticosteroid administration, is a documented cause of hyperlipidemia in dogs.[1–4,30,32,33] One reference suggests that hyperlipidemia associated with hyperadrenocorticism may result from down-regulation of LDL receptors and decreased liver uptake of plasma LDL that can develop as a consequence of reduced bil-

> *Lipid disorders are divided into primary and secondary causes that develop as a consequence of abnormal lipoprotein metabolism.*

iary excretion of steroid that may accompany hyperadrenocorticism.[4] Alternatively, insulin resistance can develop with hyperadrenocorticism, leading to impairment of lipoprotein lipase as in DM.[29] Hypercholesterolemia is more commonly reported than hypertriglyceridemia in dogs and cats with hyperadrenocorticism, and lipemia is not a typical finding.[1,3]

Adult-onset hypothyroidism and congenital hypothyroidism in a family of giant schnauzers with hypothyroid dwarfism are associated with hyperlipidemia.[34,35] Thyroxine is thought to enhance the activity of lipoprotein lipase similar to insulin, although the exact mechanism remains unknown.[8] Hypercholesterolemia is the abnormal lipid value that is typically reported. Cholesterol elevations are usually moderate, but values greater than 1,000 mg/dl are sometimes documented.[34] Hypertriglyceridemia is less common in dogs with hypothyroidism. A further indication of the association of hyperlipidemia with hypothyroidism was illustrated in a recent retrospective study that showed dogs with chronic hyperlipidemia were 3.2 times more likely to have hypothyroidism than those without chronic hyperlipidemia.[36]

Acute pancreatitis is multifaceted and complex and may result in hyperlipidemia, primarily hypertriglyceridemia. Although the explanation for this is unknown, a plausible theory for hyperlipidemia is that in addition to exocrine pancreatic damage, simultaneous islet cell destruction occurs, leading to decreased secretion of insulin and resulting in impaired activity of lipoprotein lipase.[29] Another possibility is impairment of lipoprotein lipase activity by inflammatory cytokines liberated in acute pancreatitis.[29] Lipid abnormalities include moderate to marked hypertriglyceridemia and mild to moderate hypercholesterolemia.[37] Elevated chylomicron and VLDL levels were detected via lipoprotein electrophoresis in one study.[38]

PLN and cholestatic liver diseases are recognized initiators of hyperlipidemia.[1,3,39–43] Hereditary PLN with hyperlipidemia has been documented in familial protein-losing enteropathy and PLN in soft-coated wheaten terriers, familial renal amyloidosis in Chinese shar-peis, juvenile renal disease in golden retrievers and Doberman pinschers, and familial glomerulonephropathy in Bernese mountain dogs.[39–43] Acquired PLN results from any glomerular disease leading to protein loss. PLN can result in a condition called *nephrotic syndrome*, which is characterized by hypercholesterolemia, severe hypoalbuminemia, ascites, and proteinuria. Mild hypertriglyceridemia is also reported in dogs and cats

with nephrotic syndrome.[3] The derivation of hypercholesterolemia in PLN is not fully understood but may be related to a generalized increase in protein production, including lipoproteins, by the liver in response to hypoalbuminemia.[13] Diet may also contribute to hypercholesterolemia because patients with PLN are often fed diets higher in fat.

Cholestatic liver disease, regardless of the cause, can lead to mild or moderate hypercholesterolemia.[1,4,13,29] Lipoprotein X (i.e., an abnormal lipoprotein rich in cholesterol esters and ineffective in cholesterol delivery to the liver) has been identified in experimental induction of cholestasis in rats, dogs, and pigs.[44] Lipoprotein X is also present in humans with cholestasis and is thought to contribute to hypercholesterolemia associated with cholestasis.[44] The mechanisms for increased cholesterol and formation of lipoprotein X are complex and still largely unknown. It is speculated that they occur in cholestasis from a combination of reduced excretion of biliary lipids and bile acids and increased cholesterol synthesis by the liver occurring as a result of lack of normal regulatory suppression of cholesterol production by hepatocytes.[29,44] Alleviation of cholestasis typically resolves hypercholesterolemia.

THERAPEUTICS

Because most lipid disorders in dogs arise from secondary causes, correcting or managing the secondary cause is the aim of many therapeutic regimens, which in turn should lower plasma lipid levels. However, dietary intervention is considered the most practical and efficacious treatment of hyperlipidemia, primarily hypertriglyceridemia. Placing dogs on balanced low-fat diets is the aim of this regimen.[28] Many reduced-fat diets for dogs are available on the market; however, what is most important in managing hyperlipidemia in dogs is feeding a high-quality, balanced ration that maintains dietary fat below 12% based on dry-weight matter.[15]

In human medicine, hyperlipidemia is often reduced through various "cholesterol-lowering" medications. Although these medications are not approved for use in dogs, niacin at 25 to 100 mg/day and gemfibrozil at 200 mg/day have reportedly been used in dogs.[15,28] Pruritus and erythema are two reported side effects of niacin in dogs, whereas minimal side effects of gemfibrozil have been reported.[15,28] Other lipid-reducing strategies for dogs include dietary supplementation of marine-life oil, omega-3 fatty acids, and fish oil.[28] Menhaden fish-oil capsules (which are omega-3 fatty acid rich) at a dose of

1 g/4.55 kg along with reduced dietary fat have reportedly been effective in controlling hypertriglyceridemia.[28] Interestingly, one study of the effects of fatty acid supplementation in canine renal insufficiency induced by nephrectomy showed that addition of omega-3 fatty acids lessened associated hypercholesterolemia in dogs and minimized or protected further renal impairment compared with omega-6 fatty acid supplementation.[45]

CONCLUSION

Lipid disorders are frequently reported in dogs, with most being the secondary type. A combination of clinical findings and laboratory data is often needed to diagnose such disorders, and the first indication that a problem exists is often the finding of hypercholesterolemia on a biochemical panel or lipemia in a blood sample from a fasted patient. Diagnosing lipid disorders initially involves ruling in or out known causes of secondary lipid disorders. Primary disorders should be considered after excluding secondary lipid disorders, especially in miniature schnauzers.

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1. **The diagnosis of lipid disorders in dogs should be based on**
   a. clinical assessment.
   b. biochemical analysis of the patient's blood.
   c. breed predisposition.
   d. all of the above

2. **Which plasma lipoprotein is unique in dogs?**
   a. VLDL
   b. LDL
   c. HDL_1
   d. HDL_3

3. **Dogs are more resistant than humans to atherosclerosis because dogs have**
   a. lower amounts of plasma HDL_3.
   b. no detectable activity of cholesterol ester transfer protein.
   c. higher circulating amounts of LDL.
   d. no LCAT activity.

4. **Which statement regarding plasma lipids is correct?**
   a. Lipemia always indicates hypertriglyceridemia and hypercholesterolemia.
   b. The refrigeration test can differentiate between VLDL- and LDL-induced hyperlipoproteinemia.
   c. Hyperlipidemia can be present as a result of hypercholesterolemia but not hypertriglyceridemia.
   d. Chylomicrons float to the top of lipemic plasma after 12 hours of refrigeration.

5. **Which statement(s) regarding cholesterol and triglyceride values is correct?**
   a. Cholesterol values greater than 750 mg/ml can predispose dogs to atherosclerosis despite their natural resistance.
   b. Cholesterol values are considered significantly increased if they are greater than 250 mg/dl.
   c. Triglyceride values greater than 350 mg/dl can induce plasma turbidity.
   d. a and c

6. **Lipemia can interfere with**
   a. plasma protein measurement by refractometry.
   b. total bilirubin levels.
   c. electrolyte levels.
   d. all of the above

7. **Thyroxine and insulin both enhance the effect of**
   a. cholesterol ester transfer protein.
   b. LCAT.
   c. lipoprotein lipase.
   d. none of the above

8. **Which endocrine disorder(s) is associated with hyperlipidemia in dogs?**
   a. hypothyroidism
   b. hyperadrenocorticism
   c. DM
   d. all of the above

9. **Nephrotic syndrome (a severe form of PLN) is a documented cause of hyperlipidemia. Characteristics of this syndrome include _____ ascites, and proteinuria.**
   a. hypertriglyceridemia, hypoalbuminemia,
   b. hypercholesterolemia, hypoalbuminemia,
   c. hypercholesterolemia, hyperalbuminemia,
   d. hypertriglyceridemia, hyperalbuminemia,

10. **Treating secondary lipid disorders in dogs typically involves**
    a. managing the underlying medical condition and placing dogs on a reduced-fat diet.
    b. no medical intervention because secondary lipid disorders usually resolve without treatment.
    c. immediately placing patients on cholesterol-lowering pharmaceuticals such as niacin or gemfibrozil.
    d. none of the above