Lipid metabolism and hyperlipidemia in dogs

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Lipid metabolism in dogs can be divided into exogenous and endogenous pathways and exhibits some unique characteristics compared to other species. Hyperlipidemia is common in dogs, and can be either primary or secondary to other diseases. Secondary hyperlipidemia is the most common form and can be a result of endocrine disorders, pancreatitis, cholestasis, protein-losing nephropathy, obesity, and high fat diets. Primary hyperlipidemia is less common and usually associated with certain breeds. Hypertriglyceridemia of Miniature Schnauzers is the most common type of primary hyperlipidemia in dogs in the United States, and appears to have a genetic basis although its etiology remains unknown. Possible complications of canine hyperlipidemia include pancreatitis, liver disease, atherosclerosis, ocular disease, and seizures. Management is achieved by administration of low fat diets with or without the administration of lipid-lowering agents such as omega-3 fatty acids, gemfibrozil, and niacin.

Introduction

Lipids are water-insoluble organic compounds, which are essential for many normal functions of living organisms: they are important components of cell membranes, they are used to store energy, and they play a significant role as enzyme co-factors, hormones, and intracellular messengers (Rifai et al., 1999). Of the many groups of lipids, three are most important from a clinical perspective: fatty acids, sterols (mainly cholesterol), and acylglycerols (mainly triglycerides) (Ginsberg, 1998; Rifai et al., 1999).

Fatty acids are relatively simple lipids and are also important components of many other lipids (Ginsberg, 1998; Rifai et al., 1999). Cholesterol is the main sterol in animal tissues. Dietary intake is the major source of cholesterol, but it can also be synthesized endogenously by the liver and other tissues. It plays a fundamental role in central metabolic pathways, such as bile acid metabolism and steroid hormone and vitamin D synthesis (Ginsberg, 1998; Rifai et al., 1999). Triglycerides are the most common and efficient form of stored energy in mammals. They can be derived from both dietary sources and endogenous (hepatic) production (Ginsberg, 1998; Rifai et al., 1999).

Because lipids are water-insoluble molecules, they cannot be transported in aqueous solutions, such as plasma. For that reason, lipids are transported in plasma as macromolecular complexes known as lipoproteins (Mahley and Weisgraber, 1974; Whitney, 1992; Watson and Barrie, 1993; Ginsberg, 1998; Rifai et al., 1999; Bauer, 2004; Johnson, 2005). Lipoproteins are spherical structures that consist of a hydrophobic core containing lipids (i.e. triglycerides and/or cholesterol esters), and an amphiphilic (i.e. both hydrophobic and hydrophilic) outer layer of phospholipids, free cholesterol, and proteins that forms a protective envelope surrounding the lipid core (Mahley and Weisgraber, 1974; Bauer, 1996, 2004; Ginsberg, 1998; Rifai et al., 1999; Johnson, 2005). It is worth noting that free fatty acids are transported bound to albumin and do not require incorporation into lipoproteins for transport (Whitney, 1992; Watson and Barrie, 1993; Ginsberg, 1998; Rifai et al., 1999; Bauer, 2004; Johnson, 2005).

Plasma lipoproteins differ in their physical and chemical characteristics such as size, density, and composition. Canine lipoproteins can be divided based on their hydrated density into four major classes (Table 1): (1) chylomicrons, (2) very low-density lipoproteins (VLDL), (3) low-density lipoproteins (LDL), and (4) high-density lipoproteins (HDL) (Bauer, 1992; Watson and Barrie, 1993; Maldonado et al., 2001). HDL can be further subdivided into HDL1, which is unique to dogs, HDL2, and HDL3 (Mahley and Weisgraber, 1974; Bauer, 1992, 2004; Watson and Barrie, 1993; Ginsberg, 1998; Rifai et al., 1999; Johnson, 2005). In humans, intermediate density lipoproteins (IDL) have been identified, but their existence has not been verified in dogs (Mahley and Weisgraber, 1974; Bauer, 1992, 2004; Watson and Barrie, 1993; Ginsberg, 1998; Rifai et al., 1999; Johnson, 2005).

The proteins that are part of the lipoproteins are known as apolipoproteins (or apoproteins) and play a significant role in lipid transport and metabolism (Table 2) (Ginsberg, 1998; Rifai et al., 1999; Bauer, 2004; Johnson, 2005). Lipoproteins can contain one or a variety of apolipoproteins, which regulate their metabolic functions (Bauer, 2004). In general, apolipoproteins are involved
in several physiological functions of lipoproteins such as facilitation of lipid transport, maintenance of structural integrity, and activation of certain enzymes that play key roles in lipid metabolism (Table 2) (Ginsberg, 1998; Rifai et al., 1999; Bauer, 2004; Johnson, 2005).

Lipoprotein lipase is an enzyme that is located on the luminal surface of the capillary endothelial cells, and hydrolyzes triglycerides within lipoproteins into free fatty acids, mono- and diglycerides, and glycerol (Wang and Hartsuck, 1992). Apolipoprotein C-II is an important co-factor of lipoprotein lipase (Wang and Hartsuck, 1992; Ginsberg, 1998; Rifai et al., 1999; Bauer, 2004; Johnson, 2005). Hepatic triglyceride lipase, also known as hepatic lipase, is located on endothelial cells of hepatic sinusoids and several extrahepatic tissues, and is involved in hepatic uptake of triglycerides and phospholipids from chylomicrons and VLDL remnants, the conversion of HDL2 to HDL3 (Connelly, 1999).

Lecithin–cholesterol acyl transferase (LCAT) circulates in the blood mainly bound to HDL (Fielding and Fielding, 1995; Jonas, 2000). LCAT acts on HDL molecules to convert cholesterol into cholesterol esters, and plays a crucial role in a pathway known as reverse cholesterol transport (Fielding and Fielding, 1995; Jonas, 2000; Bauer, 2004; Johnson, 2005). In humans, an additional enzyme, cholesteryl ester transfer protein (CETP), is involved in lipid metabolism. The role of this enzyme is to transfer triglycerides from VLDL and chylomicrons to HDL2 and cholesteryl esters from HDL2 to VLDL and LDL (Deckelbaum et al., 1982; Fielding and Fielding, 1995; Ginsberg, 1998; Johnson, 2005). CETP activity has not been documented in dogs (Tsutsumi et al., 2001; Bauer, 2004; Johnson, 2005). As a result, canine HDL2 molecules continue to acquire cholesteryl esters produced by LCAT leading to the formation of the unique HDL1 molecules (Bauer, 2004; Johnson, 2005).

Lipid metabolism

Lipid metabolism can be divided into two basic pathways: the exogenous pathway, which is associated with the metabolism of exogenous (dietary) lipids, and the endogenous pathway, which is associated with the metabolism of endogenously produced lipids (Ginsberg, 1998; Rifai et al., 1999; Bauer, 2004).

Exogenous pathway

The first step in dietary lipid metabolism is digestion (Bauer, 1996; Guyton and Hall, 2000). Dietary lipids that reach the duodenum undergo emulsification and are then hydrolyzed by the pancreatic and intestinal lipases (Bauer, 1996; Steiner, 2000; Guyton and Hall, 2000). Hydrolysis products (mainly free fatty acids and monoglycerides) are then transferred to the microvilli of the intestinal epithelial cell brush border in the form of micelles, where they diffuse through the epithelial cell membranes into the intestinal mucosal cells (Bauer, 1996; Guyton and Hall, 2000). In the intestinal mucosal cell, free fatty acids and monoglycerides resemble to form triglycerides, which then combine with phospholipids, free and esterified cholesterol, and the apolipoprotein (apo) B48 to form chylomicrons (Bauer, 1995, 1996, 2004; Ginsberg, 1998; Rifai et al., 1999).

Chylomicrons are the lipoprotein class responsible for transfer of dietary lipids. After formation in the enterocytes, chylomicrons, which mainly contain triglycerides, are secreted into the lacteals and enter first the lymphatic and later the blood circulation where they acquire apolipoproteins C and apo E from circulating HDL molecules (Bauer, 1995, 1996, 2004; Ginsberg, 1998; Rifai et al., 1999). Apolipoprotein C-II, which is exposed on the chylomicron surface, activates the lipoprotein lipase attached to the capillary beds in adipose and skeletal muscle tissues, which then hydrolyzes triglycerides into free fatty acids and glycerol (Bauer, 1995, 1996, 2004; Ginsberg, 1998; Rifai et al., 1999). Free fatty acids enter the muscle cells (where they are used for energy production) and/or adipocytes (where they are re-esterified into triglycerides for storage). The cholesterol-rich remaining particles (chylomicron remnants), return their apo C-II molecule to HDL and are recognized by specific hepatic apo E receptors that rapidly remove them from the circulation by endocytosis (Bauer, 1995, 1996, 2004; Ginsberg, 1998; Rifai et al., 1999). The cholesterol found in chylomicron remnants can be used for lipoprotein (VLDL) and/or bile acid formation, or stored as cholesteryl esters (Bauer, 1995, 1996).

Endogenous pathway

While chylomicrons are responsible for transport of dietary lipids, VLDL, LDL, and HDL are mainly involved in the metabolism of endogenously produced lipids (Bauer, 1996). Endogenously synthesized triglycerides and cholesterol (and cholesteryl esters) combine...
bile with phospholipids, apo B100, and apo B48 to form VLDL (Bauer, 1996, 2004; Ginsberg, 1998; Rifai et al., 1999). After VLDL molecules reach the vasculature, they acquire apolipoproteins C and apo E from HDL (Bauer, 1995, 2004; Ginsberg, 1998; Rifai et al., 1999). VLDL apo C-II activates lipoprotein lipase located in the capillary beds, which in turn leads to hydrolysis of VLDL triglycerides and the production of free fatty acids and glycerol. The VLDL molecules remaining after hydrolysis of VLDL triglycerides (VLDL remnants) are either removed from the circulation by the liver or undergo further transformation by lipoprotein lipase and/or hepatic lipase to form LDL (Bauer, 1995, 1996, 2004; Ginsberg, 1998; Rifai et al., 1999; Johnson, 2005).

LDL, which contains mainly cholesteryl esters and phospholipids, circulates in the blood and binds to specific receptors that are widely distributed throughout tissues in order to deliver cholesterol, which can be used for the synthesis of steroid hormones and cell membranes as well as for hepatic metabolism (Bauer, 1996; Ginsberg, 1998; Rifai et al., 1999).

HDLs, which are synthesized primarily in the liver, play an important role as donors and acceptors of apolipoproteins C, apo E, and various lipids from other lipoproteins in the circulation (Watson and Barrie, 1993; Ginsberg, 1998; Rifai et al., 1999; Bauer, 2004). They also have a critical role in the reverse cholesterol transport pathway, through which cholesterol is transferred from peripheral tissues to the small circulating discoid HDL molecules, thus converting them to nascent HDL3 molecules (Watson and Barrie, 1993; Fielding and Fielding, 1995; Ginsberg, 1998; Bauer, 2004). HDL cholesterol is then esterified by the action of LCAT and the resulting cholesteryl esters move to the core of the HDL molecule thus allowing more free cholesterol to be absorbed into their surface. Continued absorption of free cholesterol and subsequent esterification by LCAT leads to the formation of the larger, cholesteryl ester-rich HDL2.

In dogs, due to absence of the enzyme CETP (which is present in humans), HDL3 molecules continuously acquire cholesteryl esters, resulting in the formation of the unique HDL2 molecules. On HDL2, cholesteryl esters are transferred from tissues to the liver for disposal or reuse, and not to LDL or VLDL molecules (as in humans), which transfer cholesterol to peripheral tissues (Watson and Barrie, 1993; Bauer, 2004; Johnson, 2005). It has been suggested that it is this function of HDL2 that accounts for the lower incidence of atherosclerotic disorders in dogs compared to humans (Johnson, 2005).

Disorders of lipid metabolism

Definitions

The term hyperlipidemia refers to increased concentrations of lipids (triglycerides, cholesterol, or both) in the blood (Watson and Barrie, 1993; Ford, 1996; Johnson, 2005). Increased blood concentrations of triglycerides are referred to as hypertriglyceridemia, while increased blood concentrations of cholesterol are referred to as hypercholesterolemia. The term hyperlipoproteinemia refers to increased blood concentrations of lipoproteins, but it is often used interchangeably with the term hyperlipidemia. However, the term hyperlipoproteinemia should ideally be used only in cases where measurement of actual lipoproteins has been performed (Bauer, 1995; Johnson, 2005).

The term lipemia is used to describe turbid or lacescent appearance of serum or plasma (Watson and Barrie, 1993; Ford, 1996; Johnson, 2005). Lipemia is a result of hypertriglyceridemia, but not hypercholesterolemia (Watson et al., 1993; Bauer, 1995; Ford, 1996; Johnson, 2005). However, mild hypertriglyceridemia also does not cause lipemia. Usually, lipemia is apparent when serum triglyceride concentrations exceed 2.26 mmol/L (200 mg/dL) (Bauer, 1995). As serum triglyceride concentrations increase, serum becomes turbid (cloudy) and then lacescent (milky).

Laboratory evaluation of lipid disorders

Serum turbidity

Visual evaluation of plasma or serum usually offers the first estimate of a sample’s triglyceride concentration. Samples that have normal or near normal serum triglyceride concentrations are clear, while samples with increased serum triglyceride concentrations are lipemic (turbid or lacescent; Fig. 1) (Watson and Barrie, 1993; Ford, 1996; Johnson, 2005). In general, turbidity appears when serum triglyceride concentrations are 2.26–3.39 mmol/L (200–300 mg/dL), and lacescent serum is seen when serum triglyceride concentrations are 11.3 mmol/L (1000 mg/dL) (Bauer, 1995; Johnson, 2005). However, these guidelines provide only a rough estimate of the actual serum triglyceride concentration and measurement of the actual serum triglyceride concentration is required. In addition, the presence or absence of hypercholesterolemia cannot be based on serum appearance, because hypercholesterolemia does not cause increased serum turbidity (Whitney, 1992; Johnson, 2005).

Chylomicron test

The chylomicron (or refrigeration) test is performed on lipemic samples and is a simple method to determine the specific form of lipoprotein that is responsible for hypertriglyceridemia (Rogers, 1977; Whitney, 1992; Johnson, 2005). Serum samples are refrigerated and left undisturbed for 10–12 h. Due to their lower density, chylomicrons tend to move to the top of the sample and form a ‘cream layer’ (Fig. 2). When a cream layer is formed, then chylomicrons are in excess in the sample and account (partially or solely) for the hypertriglyceridemia. If there is no cream layer formation, the hypertriglyceridemia and lipemia are due to excess of other lipoproteins (usually VLDL). When a cream layer forms, the serum below the cream layer can either be clear or turbid. In the first case, hyperchylomicronemia is most likely solely responsible for the hypertriglyceridemia, while in the second case other lipoproteins are also present in excess (Fig. 2) (Whitney, 1992; Johnson, 2005).

Methods for quantification and characterization of lipids in blood

Routine quantitative assessment of total cholesterol and triglyceride concentrations in serum or plasma is usually achieved by use of spectrophotometric or enzymatic methods (Nelson et al., 2004). Other methods (e.g., lipoprotein electrophoresis, ultracentrifugation) have also been used but have limited use in the routine clinical evaluation of hyperlipidemic dogs (Whitney, 1992; Nelson et al., 2004).

Interference with laboratory measurements

It is important to note that lipemia can often interfere with the determination of several analytes, depending on the methodology and analyzer used. Analytes the determination of which has been reported to be affected by lipemia (i.e., falsely increased or decreased) include, but are not limited to, bilirubin, liver enzymes, amylase, lipase, electrolytes, protein, albumin, and glucose (Nelson et al., 2004).

Causes of hyperlipidemia

Postprandial hyperlipidemia is physiological and transient, and typically resolves within 7–12 h after a meal, depending on the fat content of the meal (Whitney, 1992; Downs et al., 1997; Bauer, 2004; Johnson, 2005). For that reason, any determination of serum lipid concentrations should always follow a fast of at least 12 h.
Fig. 1. Lipemia. Serum samples with normal triglyceride concentrations are clear (left tube). As the serum triglyceride concentration increases, serum becomes turbid (middle tube) and ultimately lactescent (right tube).

Fig. 2. Chylomicron test. The picture on the left shows a lipemic serum sample from a dog with hypertriglyceridemia right after separation of the serum from the clot. The same serum sample is shown on the right after overnight refrigeration (chylomicron test). The formation of a cream layer due to hyperchylomicronemia is obvious. The remaining serum below the cream layer is clear (although hemolytic), which suggests that other classes of lipoproteins are not increased in this patient.
Persistent fasting hyperlipidemia is always considered abnormal and can be either secondary to other diseases or drug administration, or primary (Table 3).

Secondary causes of hyperlipidemia in dogs

Secondary hyperlipidemia is the most common pathologic form of hyperlipidemia in dogs (Nelson et al., 2004). Several diseases have been reported to cause hyperlipidemia.

Endocrine disease

Most commonly, canine hyperlipidemia is the result of an endocrine disorder, such as hypothyroidism, diabetes mellitus, or hyperadrenocorticism (Rogers et al., 1975b; Rogers, 1977; Whitney, 1992; Bauer, 2004; Feldman and Nelson, 2004; Johnson, 2005). Increases in both serum triglyceride and cholesterol concentrations have been reported in dogs with hypothyroidism (Rogers et al., 1975b; Barrie et al., 1993; Panciera, 1994; Dixon et al., 1999; Schenck et al., 2004). In one study, hypertriglyceridemia and hypercholesterolemia were found in 88% and 78% of dogs with hypothyroidism, respectively (Dixon et al., 1999). Usually, lipid abnormalities resolve after treatment of hypothyroidism (Rogers et al., 1975b).

In dogs with diabetes mellitus, hyperlipidemia is most commonly associated with hypertriglyceridemia but hypercholesterolemia might also be present (Rogers et al., 1975b; Wilson et al., 1986; Whitney, 1992; Barrie et al., 1993; Feldman and Nelson, 2004; Johnson, 2005). Similarly, hypertriglyceridemia usually resolves after successful treatment of diabetes but hypercholesterolemia might persist despite therapy (Gleeson et al., 1990; Whitney, 1992).

Finally, both naturally occurring and iatrogenic hyperadrenocorticism have been associated with hyperlipidemia (hypertriglyceridemia and hypercholesterolemia) in dogs (Ling et al., 1979; Whitney, 1992; Barrie et al., 1993; Huang et al., 1999; Bauer, 2004; Feldman and Nelson, 2004; Johnson, 2005). Hypertriglyceridemia might be present more frequently than hypercholesterolemia, and increases in both types of lipids are usually mild or moderate (Bauer, 2004; Feldman and Nelson, 2004; Johnson, 2005).

Pancreatitis

The presence of hyperlipidemia (hypertriglyceridemia and, to a lesser degree, hypercholesterolemia) has long been associated with naturally occurring pancreatitis in dogs (Anderson and Low, 1965; Anderson and Strafuss, 1971; Rogers et al., 1975b; Rogers, 1977; Whitney, 1992; Cook et al., 1993; Hess et al., 1998, 1999; Bauer, 2004; Williams and Steiner, 2005; Johnson, 2005). However, it remains uncertain whether hyperlipidemia develops as a result of pancreatitis or can be the cause of pancreatitis in some cases (Whitney, 1992; Williams and Steiner, 2005).

In models of experimentally induced pancreatitis in dogs, hyperlipidemia did not occur after induction of pancreatitis (Bass et al., 1976; Whitney et al., 1987; Chikamune et al., 1998). However, no conclusive statement regarding the role of naturally occurring pancreatitis in the development of secondary hyperlipidemia can be made. It is possible that either hyperlipidemia is a pre-existing abnormality in some dogs with naturally occurring pancreatitis, which might or might not contribute to the development of pancreatitis, or that naturally occurring pancreatitis differs from the experimental models of pancreatitis used in the above studies in its ability lead to hyperlipidemia.

Obesity

Increased serum triglyceride and/or cholesterol concentrations have been observed in obese dogs (Chikamune et al., 1995; Bailhache et al., 2003; Jeusette et al., 2005). The most profound changes were associated with severe chronic obesity (Jeusette et al., 2005). Weight loss in obese dogs leads to significant decreases in both serum triglyceride and cholesterol concentrations (Diez et al., 2004; Jeusette et al., 2005).

Protein losing nephropathy (PLN)

Proteinuria associated with PLN, regardless of the cause, is often associated with hyperlipidemia in dogs. The most commonly reported lipid abnormality in dogs with PLN is hypercholesterolemia, which is usually mild or moderate (Center et al., 1987; Dibartola et al., 1989, 1990; Cook and Cowgill, 1996; Littman et al., 2000). Hypercholesterolemia is usually part of a more complex syndrome, the nephrotic syndrome, which in addition to hypercholesterolemia, is characterized by hypoalbuminemia, proteinuria, and ascites (Bauer, 2004; Johnson, 2005). Hypercholesterolemia has been reported in varying frequencies in dogs with acquired glomerular disease and proteinuria, as well as in several hereditary forms of PLN (e.g., in Chinese Shar-pei and Golden Retrievers) (Center et al., 1987; Dibartola et al., 1989, 1990; Cook and Cowgill, 1996; Littman et al., 2000).
Primary causes of hyperlipidemia in dogs

Primary lipid abnormalities appear to be relatively uncommon in dogs and are usually, but not always, associated with specific breeds.

Primary (idiopathic) hyperlipidemia in Miniature Schnauzers

Primary hyperlipidemia in Miniature Schnauzers was the first breed-related primary lipid disorder described in dogs (Rogers et al., 1975a; Whitney, 1992; Ford, 1993; Whitney et al., 1993; Bauer, 1995, 2004). This condition was first reported more than 30 years ago in Miniature Schnauzers in the United States, but has not been documented elsewhere (Rogers et al., 1975a; Whitney, 1992; Ford, 1993; Whitney et al., 1993). It is characterized by abnormal accumulation of VLDL or a combination of VLDL and chylomicrons. Although hypercholesterolemia may also be present, this finding is not consistent (Whitney, 1992; Ford, 1993; Whitney et al., 1993).

A recent study has shown that primary hypertriglyceridemia is common in healthy Miniature Schnauzers in the United States, as fasting hypertriglyceridemia was found in 32.8% of 192 healthy Miniature Schnauzers investigated (Xenoulis et al., 2007). However, hypertriglyceridemia was much more prevalent among older dogs; >75% of healthy Miniature Schnauzers aged 9 years of age had hypertriglyceridemia. In addition, the severity of hypertriglyceridemia increased with age; the vast majority (>80%) of Miniature Schnauzers with moderate to severe hypertriglyceridemia were 6 years or older (Xenoulis et al., 2007). There was no difference between male and female Miniature Schnauzers with regards to the prevalence of hypertriglyceridemia. These findings likely classify hypertriglyceridemia of Miniature Schnauzers as the most common primary lipid disorder in dogs.

It is recommended that all Miniature Schnauzers in the United States should potentially be evaluated for hypertriglyceridemia while they are healthy because this information can be useful for the avoidance of misinterpretation of increased serum triglyceride concentrations when the dogs are presented sick (Xenoulis et al., 2007). In addition, by knowing the serum triglyceride status of the dog, veterinarians might consider offering low fat diets to affected dogs in order to avoid possible complications of hypertriglyceridemia. Due to the fact that hypercholesterolemia was found only in association with hypertriglyceridemia, the presence of hypercholesterolemia alone in Miniature Schnauzers might require additional diagnostic investigation.

The cause of primary hypertriglyceridemia in Miniature Schnauzers is unknown. The fact that hypertriglyceridemia is prevalent within a single breed suggests a possible hereditary cause (Rogers et al., 1975a; Ford, 1993; Whitney et al., 1993). Because lipoprotein lipase is the major enzyme involved in triglyceride clearance, deficiency of this enzyme has been considered as a possible cause of hypertriglyceridemia in this breed. However, a study in Miniature Schnauzers with hypertriglyceridemia and pancreatitis failed to identify any mutations of the lipoprotein lipase gene, suggesting that inherited lipoprotein lipase dysfunction is not the cause of hypertriglyceridemia in this breed (Schickel, 2005). In that particular study, however, dogs had both hypertriglyceridemia and pancreatitis, and the hypertriglyceridemia might have been a result of pancreatitis rather than the primary condition. In a more recent study, the gene encoding apo C-II (which is an activator of lipoprotein lipase) was evaluated for the presence of possible mutations in Miniature Schnauzers with primary hypertriglyceridemia. However, we have not been able to identify mutations that co-segregated with hypertriglyceridemia (unpublished data). Further studies are warranted to identify the genetic basis of primary hypertriglyceridemia in Miniature Schnauzers.

Until recently, primary hypertriglyceridemia was considered to be a relatively benign condition in Miniature Schnauzers. However, recent evidence suggests that it might not be as benign as initially thought. Recent studies indicate that hypertriglyceridemia in Miniature Schnauzers might be associated with pancreatitis, hepatobiliary disease, ocular disease, seizures, and possibly other conditions (see clinical signs and complications of hyperlipidemia).

Primary hyperlipidemia in other dog breeds

Primary hypercholesterolemia without hypertriglyceridemia has been documented in 15 Briards from the United Kingdom (Watson et al., 1993). A similar condition has been described in a family of rough Collies also from the UK (Jeusette et al., 2004). A slightly different condition of primary hypercholesterolemia with or without concurrent hypertriglyceridemia has been reported in Shetland Sheepdogs (Sato et al., 2000). The cause of these lipid abnormalities that mainly involved cholesterol metabolism was not determined in the above mentioned studies, but hereditary factors were suspected (Watson et al., 1993; Sato et al., 2000; Jeusette et al., 2004). In addition, primary hypercholesterolemia has been reported anecdotally in Doberman Pinschers and Rottweilers (Armstrong and Ford, 1989).

Primary hyperlipidemia with hypercholesterolemia and hypertriglyceridemia has been reported in two related Beagles (Wada et al., 1977). Finally, primary hypertriglyceridemia has been reported in two related Brittany Spaniels and one mixed-breed 28-day old puppy (Baum, 1969; Hubert et al., 1987).

Clinical signs and complications of hyperlipidemia

In general, animals with secondary hyperlipidemia display clinical signs associated with the primary disorder. Animals with primary lipid disorders are often asymptomatic for long periods or throughout their lives, depending on many factors including the type and severity of hyperlipidemia. However, in some cases, animals with hyperlipidemia develop secondary diseases as a result of hyperlipidemia that may account for the development of specific clinical signs.

Pancreatitis

An association between hyperlipidemia and pancreatitis was first noted in humans by Speck in 1865 (Speck, 1865). Today, severe hypertriglyceridemia is a known risk factor for pancreatitis in humans (Cameron et al., 1974; Toskes, 1990; Fortson et al., 1995; Yadav and Pitchumoni, 2003). An increased risk for pancreatitis from hyperlipidemia has been shown to exist when serum triglyceride concentrations exceed 11.3 mmol/L (1000 mg/dL). Hypercholesterolemia does not constitute a risk factor for pancreatitis in humans (Toskes, 1990). The mechanism by which hypertriglyceridemia induces pancreatitis is not clear, but it has been suggested that serum triglycerides are hydrolyzed by the action of pancreatic lipase, leading to excessive production of free fatty acids, which are toxic to the pancreas (Havel, 1969; Saharia et al., 1977).

A similar relationship between hypertriglyceridemia and pancreatitis has been suggested in dogs (Rogers et al., 1975a; Rogers, 1985; Whitney et al., 1993). However, because hypertriglyceridemia is often associated with hypercholesterolemia in dogs, the risk of pancreatitis in dogs with hypertriglyceridemia is difficult to determine. In a recent study, the gene encoding apo C-II was evaluated for the presence of possible mutations in Miniature Schnauzers with primary hypertriglyceridemia. However, we have not been able to identify mutations that co-segregated with hypertriglyceridemia (unpublished data). Further studies are warranted to identify the genetic basis of primary hypertriglyceridemia in Miniature Schnauzers.
in dogs: vacuolar hepatopathy and gallbladder mucocele (Center, 1996; Scherk and Center, 2005). Hyperlipidemia-associated vacuolar hepatopathy has been more commonly associated with hypertriglyceridemia in Miniature Schnauzers (Center, 1996). Gallbladder mucocele has been commonly reported in dog breeds that are predisposed to idiopathic hyperlipidemia (e.g., Miniature Schnauzers and Shetland Sheepdogs) and hyperlipidemia has been implicated in gallbladder disease in humans (Boland et al., 2002; Whitney et al., 1992; Ford, 1996). This is highly speculative, however, because published reports are lacking and, given the difficulty in diagnosing pancreatitis especially in past decades, pancreatitis could have easily been missed.

**Atherosclerosis**

Although dogs appear to be resistant to atherosclerosis due to their lipoprotein composition and metabolism, they have been reported to develop atherosclerosis in both experimental and clinical studies (Ford, 1996; Whitney, 1992; Ford, 1996; Williams and Steiner, 2005). Available clinical and experimental data to support the above hypotheses are limited, however. Pancreatitis has been shown to develop in dogs after feeding high fat, low protein diets, and is more severe when induced in dogs being fed a high fat diet (Lindsay et al., 1948; Goodhead, 1971). Also, in vitro studies on an isolated canine pancreas showed that high triglyceride concentrations can induce pancreatitis possibly through the release of free fatty acids (Saharia et al., 1977).

Clinical studies have shown an association between hypertriglyceridemia and pancreatitis in dogs, although it is not known whether hypertriglyceridemia was the cause or a result of pancreatitis, or just an incidental finding in some cases (Ford, 1996; Williams and Steiner, 2005). In a preliminary study, hypertriglyceridemia exceeding 10.17 mmol/L (500 mg/dL) was found to be associated with an increased risk for pancreatitis in Miniature Schnauzers, and that might also be true for dogs of other breeds (Xenoulis et al., 2006). Secondary hyperlipidemia seen in dogs with some endocrinopathies (e.g., hyperadrenocorticism) or obesity may be responsible for the increased risk for pancreatitis associated with these diseases (Chikamune et al., 1995; Hess et al., 1999, 2000). Based on these studies, an association between hypertriglyceridemia and pancreatitis in dogs is obvious, but a cause-and-effect relationship has not been established yet.

**Hepatobiliary disease**

Clinical studies and anecdotal observations suggest that two conditions of the liver might be associated with hypertriglyceridermia in dogs: vacuolar hepatopathy and gallbladder mucocele (Center, 1996; Scherk and Center, 2005). Hyperlipidemia-associated vacuolar hepatopathy has been more commonly associated with hypertriglyceridemia in Miniature Schnauzers (Center, 1996). Gallbladder mucocele has been commonly reported in dog breeds that are predisposed to idiopathic hyperlipidemia (e.g., Miniature Schnauzers and Shetland Sheepdogs) and hyperlipidemia has been implicated in gallbladder disease in humans (Boland et al., 2002; Pike et al., 2004; Aguirre et al., 2007). In a recent study, an association between gallbladder mucocele formation and dyslipidemias (hypertriglyceridermia and hypercholesterolemia) was described in Shetland Sheepdogs (Aguirre et al., 2007). In this study, many of the dogs with a gallbladder mucocele had no clinical signs or biochemical abnormalities, except for an increased serum ALP activity in some cases (Aguirre et al., 2007). Although asymptomatic in many cases, both vacuolar hepatopathy and gallbladder mucocele can potentially be fatal (Center, 1996; Scherk and Center, 2005).

Idiopathic hypertriglyceridemia (especially \( \geq 4.52 \text{ mmol/L} \) or \( 400 \text{ mg/dL} \)) was found to be associated with increased serum liver enzyme activities in healthy Miniature Schnauzers (Xenoulis et al., 2008). In that study, 60% and 45% of the Miniature Schnauzers with serum triglyceride concentrations \( \geq 4.52 \text{ mmol/L} \) (400 mg/dL) had increased ALP and ALT activities, respectively. In contrast, 0% and 9% of the Miniature Schnauzers with normal serum triglyceride concentrations had increased ALP and ALT activities, respectively. Whether or not such cases require additional diagnostic investigation of the cause of the liver disease remains to be determined. Given the fact that in this study most dogs had serum elevations of more than one liver enzyme activities that are often considered significant (\( >2 \) times the upper limit of the reference range), additional diagnostic work-up or retesting would seem appropriate.

**Ocular disease**

Several ocular manifestations of hyperlipidemia, such as lipemia retinalis, lipemic aqueous, and lipid keratopathy have been reported in dogs (Crispin, 1993). Recently, solid intraocular xanthogranuloma formation was reported as a unique disorder of hyperlipidemic Miniature Schnauzers (Zafross and Dubielzig, 2007).

Other possible complications of hyperlipidemia

Seizures and other neurologic signs have been reported to occur potentially as a result of hyperlipidemia in dogs (Rogers et al., 1975a, b; Whitney et al., 1987; Cook et al., 1993; Hess et al., 1998, 1999; Williams and Steiner, 2005). After secondary causes of hyperlipidemia have been ruled out, a presumptive diagnosis of a primary lipid disorder can be made (Whitney, 1992). It has been recommended that hypertriglycerideremia that exceeds 5.65 mmol/L (500 mg/dL) should be treated in order to avoid possible complications (Whitney, 1992; Ford, 1996). It also has been recommended that the treatment goal should be to keep serum triglyceride concentrations \(< 5.65 \text{ mmol/L} \) (500 mg/dL) (Ford, 1996). Primary hypercholesterolemia is usually associated with less severe complications compared to hypertriglycerideremia. Attempts for correction of hypercholesterolemia should have as a target to lower serum cholesterol concentrations below 500 mg/dL (13 mmol/L).

**Dietary management**

Typically, the first step in the management of primary hyperlipidemia is dietary modification (Rogers, 1977; Whitney, 1992; Ford,
Dogs with primary hyperlipidemia should be offered a low fat diet throughout their lives (Ford, 1996). Diets that contain less than 20 grams of fat per 1000 kcal are recommended (Ford, 1996; Johnson, 2005; Elliott, 2005). Many commercially available diets are suitable for dogs with primary hyperlipidemia. Treats and table scraps should be avoided unless they are low in fat (Elliott, 2005).

Surgical serum lipid concentrations should be re-evaluated after feeding a low fat diet for about 4–8 weeks (Ford, 1996). If serum triglyceride concentration has decreased to <5.5 mmol/L (500 mg/dL), dietary therapy should be continued and the new diet should be offered for the rest of the animal's life, and serum triglyceride concentrations should be re-evaluated every 6–12 months (Ford, 1996). In dogs that do not sufficiently respond to low fat diets, an ultra low fat home-made diet (e.g., 10–12 grams of fat per 1000 kcal) can be offered, or medical treatment can be initiated (Elliott, 2005).

Medical management

Some dogs with primary hyperlipidemia will not sufficiently respond to feeding a low or extra low fat diet alone, especially when hyperlipidemia due to endogenously formed lipids is present (Ford, 1993, 1996; Watson and Barrie, 1993; Bauer, 1995). In these cases, medical treatment is required in addition to the low fat diet in an effort to effectively reduce serum lipid concentrations (Ford, 1993; Watson and Barrie, 1993).

Polyunsaturated fatty acids of the n–3 series (omega-3 fatty acids) are abundant in marine fish (Logas et al., 1991). Omega-3 fatty acid supplementation, usually in the form of fish-oil, has been shown to lower serum lipoprotein concentrations in humans with primary hypertriglyceridemia, normal humans, and experimental animals (Illingworth et al., 1989; Froyland et al., 1995). In a recent study in healthy dogs, fish-oil supplementation led to a significant reduction of serum triglyceride concentrations, suggesting that this supplement may play a role in the treatment of primary canine hypertriglyceridemia (LeBlanc et al., 2005). No major side effects were observed (LeBlanc et al., 2005). However, studies evaluating the efficacy of fish-oil supplementation in dogs with hyperlipidemia are lacking and clinical experience is limited.

Because side effects are rarely reported and because efficacy of omega-3 fatty acids is likely, it is recommended by some authors that fish-oil should be administered in dogs with primary hypertriglyceridemia that do not respond to a low fat diet alone (Logas et al., 1991; Bauer, 1995; Johnson, 2005; LeBlanc et al., 2005). Menhaden fish-oil capsules have been successfully used at doses ranging from 220 to 330 mg/kg of body weight once a day (Bauer, 1995; LeBlanc et al., 2005). Periodic retesting of serum triglyceride concentrations is recommended during the treatment period.

Gemfibrozil belongs to the group of fibric acid derivatives and has been reported to reduce serum triglyceride concentrations in both healthy humans and patients with hypertriglyceridemia (Spencer and Barradell, 1996; Stalenhoef et al., 2000). In dogs, its use is anecdotal and it is usually administered at a fixed dose of 200 mg/day (Bauer, 1995). Because side effects are believed to be minimal and occur rarely, gemfibrozil is commonly recommended in combination with dietary therapy when the latter fails to lower serum triglyceride concentrations below 5.65 mmol/L (500 mg/dL) (Whitney, 1992; Bauer, 1995).

Niacin is a vitamin that has been used successfully for the treatment of hyperlipidemia in humans for many years (Kashyap et al., 2002). In dogs, niacin treatment has been reported in very few patients with primary hypertriglyceridemia. Niacin reduced serum triglyceride concentrations for several months without causing any side effects (Whitney, 1992; Bauer, 1995; Johnson, 2005). However, large clinical trials regarding the efficacy and safety of niacin use in dogs with primary hypertriglyceridemia are lacking. As in humans, niacin administration in dogs is potentially associated with side effects such as erythema and pruritus (Bauer, 1995; Kashyap et al., 2002). Niacin is usually administered at the dose of 25–100 mg/day (Bauer, 1995).

Conclusions

Disorders of lipid metabolism have received limited research attention in dogs. Canine hypertriglyceridemia has been generally considered to be a relatively benign condition in most cases, but recent scientific evidence suggests that it can often be associated with diseases such as pancreatitis, hepatobiliary disease, ocular disease, and seizures. Therefore, hypertriglyceridemia should always be taken into account and appropriately treated when necessary. As new research data become available, the list of conditions that develop as a result of hyperlipidemia (mainly hypertriglyceridemia) in dogs increases. Despite this, the number of questions regarding canine hyperlipidemia that need to be answered is large. Future studies on canine hyperlipidemia should focus on defining the spectrum of conditions associated with hyperlipidemia, determining the underlying cause of idiopathic and familial forms of hyperlipidemia, and conducting clinical trials on the efficacy and safety of lipid-lowering drugs, which could greatly benefit the management of dogs with hyperlipidemia.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationships with other people or organisations that could inappropriately influence or bias the content of the paper.

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