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Review

Lipid metabolism and hyperlipidemia in dogs

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ABSTRACT

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.

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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 amphophilic (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 HDL_1 (which is unique to dogs), HDL_2, and HDL_3 (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

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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 VLDL to LDL, and the conversion of HDL_2 to HDL_3 (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 cholesteryl 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 HDL_2 and cholesteryl esters from HDL_2 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 HDL_2 molecules continue to acquire cholesteryl esters produced by LCAT leading to the formation of the unique HDL_1 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 reassemble 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) com-

Table 1
Characteristics of major canine and feline plasma lipoproteins.

Lipoprotein	Species	Major lipids	Major apolipoproteins	Size (nm)	Density (g/mL)
Chylomicron	Dog, cat	Dietary triglycerides	B, C	75–1200	<0.960
VLDL	Dog, cat	Endogenous triglycerides	B, C, E	30–80	0.93–1.006
LDL	Dog, cat	Phospholipids, cholesteryl esters	B	18–25	1.019–1.087
HDL1	Dog	Phospholipids, cholesteryl esters	A, C, E	10–35	1.025–1.100
HDL2	Dog, cat	Phospholipids	A, C, E	9–12	1.063–1.100
HDL3	Dog, cat	Phospholipids	A, C	5–9	1.100–1.210

VLDL: very low-density lipoproteins, LDL: low-density lipoproteins, HDL: high-density lipoproteins.

Table 2
Classification and properties of major human plasma apolipoproteins.

Apolipoprotein	Molecular weight	Lipoproteins	Major metabolic function
Apo AI	28,016	HDL, chylomicrons	Structural, LCAT activator
Apo AII	17,414	HDL, chylomicrons	Unknown
Apo AIV	46,465	HDL, chylomicrons	Unknown
Apo B48	264,000	Chylomicrons	Secretion of chylomicrons from intestinal mucosal cells into lacteals
Apo B100	540,000	VLDL, IDL, LDL	Secretion of VLDL from the liver, structural
Apo CI	6630	chylomicrons, VLDL, IDL, HDL	Uncertain
Apo CII	8900	chylomicrons, VLDL, IDL, HDL	Activator of lipoprotein lipase
Apo CIII	8800	chylomicrons, VLDL, IDL, HDL	Inhibitor of lipoprotein lipase
Apo E	34,145	chylomicrons, VLDL, IDL, HDL	Facilitates uptake of chylomicron remnants
Apo (a)	250,000–800,000	Lp (a)	Uncertain

Apo: apolipoprotein, HDL: high-density lipoproteins, VLDL: very low-density lipoproteins, IDL: intermediate density lipoproteins, LDL: low-density lipoproteins, Lp (a): lipoprotein a.

bine 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 HDL_3 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 HDL_2.

In dogs, due to absence of the enzyme CETP (which is present in humans), HDL_2 molecules continuously acquire cholesteryl esters, resulting in the formation of the unique HDL_1 molecules. On HDL_1, 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 HDL_1 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 lactescent 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 lactescent (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 lactescent; 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 lactescent 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.

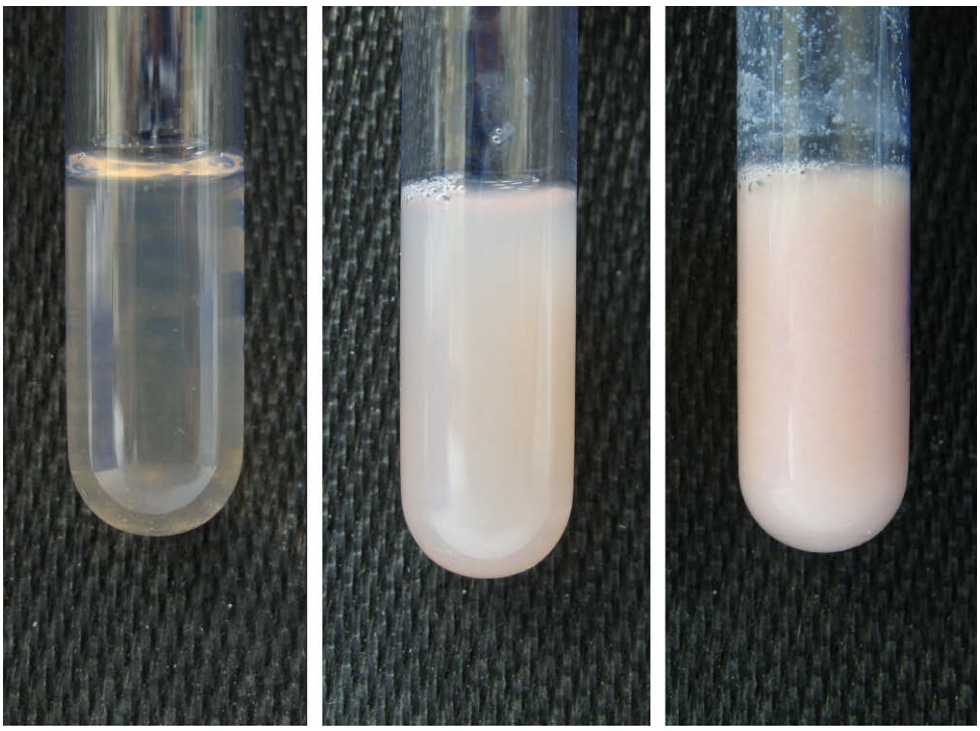

Fig. 1. Lipemia. Serum samples with normal triglyceride concentrations are clear (left tube). As the serum triglyceride concentration increases, serum becomes turbid (middle tube) and ultimately lactescent (right tube).

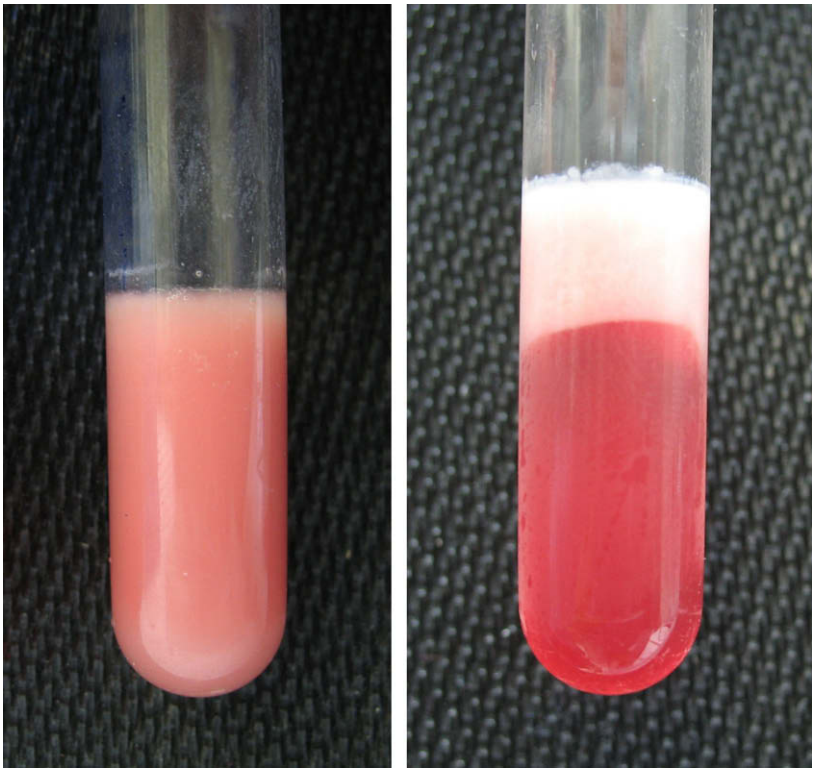

Fig. 2. Chylomicron test. The picture on the left shows a lipemic serum sample from a dog with hypertriglyceridemia right after separation of the serum from the clot. The same serum sample is shown on the right after overnight refrigeration (chylomicron test). The formation of a cream layer due to hyperchylomicronemia 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.

Table 3
Main primary and secondary lipid disorders and respective lipid and lipoprotein abnormalities in dogs.

Causes of hyperlipidemia	Lipid(s) affected (increased)	Lipoprotein class mainly affected (increased)
Primary		
Primarily triglyceride defect		
Miniature Schnauzers	Triglycerides, maybe cholesterol	VLDL, chylomicrons
Brittany Spaniels	Triglycerides	VLDL, chylomicrons
Primarily cholesterol defect		
Briards	Cholesterol	HDL1
Rough collies	Cholesterol	HDL1, VLDL, LDL
Shetland sheepdogs	Cholesterol, maybe triglycerides	HDL1, LDL
Doberman Pinschers	Cholesterol	Unknown
Rottweilers	Cholesterol	Unknown
Mixed defect		
Beagles	Triglycerides, cholesterol	HDL1, LDL
Secondary		
Pancreatitis	Triglycerides, maybe cholesterol	VLDL, chylomicrons, LDL, HDL1
Hypothyroidism	Triglycerides, cholesterol	HDL1, VLDL, LDL
Hyperadrenocorticism	Triglycerides, cholesterol	VLDL, LDL
Diabetes mellitus	Triglycerides, cholesterol	VLDL
Protein losing nephropathy	Cholesterol, maybe triglycerides	Unknown
Cholestasis	Cholesterol, triglycerides	LDL
Obesity	Triglycerides, cholesterol	VLDL, LDL, HDL
High fat diets	Triglycerides, cholesterol	HDL1

HDL: high-density lipoproteins, VLDL: very low-density lipoproteins, LDL: low-density lipoproteins.

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-peis and Golden Retrievers) (Center et al., 1987; Dibartola et al., 1989, 1990; Cook and Cowgill, 1996; Littman et al., 2000).

Cholestasis

Cholestasis has been reported to lead to mild or moderate hypercholesterolemia and mild hypertriglyceridemia in dogs (Danielsson et al., 1977; Whitney, 1992; Chuang et al., 1995). Changes in lipoproteins, mainly excessive esterification of lipoprotein cholesterol, have also been reported in dogs with experimentally induced cholestasis (Blomhoff et al., 1978; Walli and Seidel, 1984).

Other causes

Several other causes of hyperlipidemia have been reported or suspected to exist in dogs. These include high fat diets, lymphoma, infection with *Leishmania infantum*, congestive heart failure due to dilated cardiomyopathy, and administration of certain drugs (e.g., glucocorticoids) (Nieto et al., 1992; Ogilvie et al., 1994; Burkhard and Meyer, 1995; Downs et al., 1997; Tidholm and Jonsson, 1997). Finally, in a recent study, significantly increased serum triglyceride concentrations were reported in association with other lipid abnormalities in dogs with parvoviral enteritis (Yilmaz and Senturk, 2007).

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 $\geqslant$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,

1977; Whitney, 1992; Ford, 1993, 1996; Bauer, 1995, 2004; Williams, 1996; Williams and Steiner, 2005). In addition, the high prevalence of pancreatitis in Miniature Schnauzers has been attributed to the fact that dogs of this breed commonly develop hypertriglyceridemia (Whitney, 1992; Williams, 1996; 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 (Rogers et al., 1975a,b; Whitney et al., 1987; Cook et al., 1993; Hess et al., 1998, 1999; Williams and Steiner, 2005). In a preliminary study, hypertriglyceridemia exceeding 10.17 mmol/L (900 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 hypertriglyceridemia 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 (hypertriglyceridemia 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; Aguirre et al., 2007).

Idiopathic hypertriglyceridemia (especially $\geqslant$4.52 mmol/L or 400 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 $\geqslant$4.52 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.

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 (Mahley et al., 1974, 1977; Liu et al., 1986; Kagawa et al., 1998; Hess et al., 2003). Spontaneous atherosclerosis has been reported in dogs mainly in association with secondary hypercholesterolemia due to endocrinopathies (Liu et al., 1986; Hess et al., 2003). In one study, 60% of 30 dogs with atherosclerosis had hypothyroidism and 20% had diabetes mellitus (Hess et al., 2003).

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; Bodkin, 1992; Bauer, 1995; Vitale and Olby, 2007). However, the relationship between these disorders remains obscure in dogs. Also, some authors report that hyperlipidemia can cause clinical signs of abdominal pain, lethargy, vomiting, and/or diarrhea without evidence of pancreatitis or other diseases (Ford, 1993, 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.

Treatment of hyperlipidemia

The first step in the treatment of hyperlipidemia is the determination of whether the patient has a primary or a secondary lipid disorder (Rogers, 1977; Ford, 1996; Johnson, 2005). Thus, specific diagnostic investigations should be performed in order to diagnose or rule out diseases that can cause secondary hyperlipidemia. Treatment of secondary hyperlipidemia relies on the successful treatment of the primary disorder after which hyperlipidemia usually resolves (Rogers, 1977; Whitney, 1992; Ford, 1996; Johnson, 2005). Resolution of secondary hyperlipidemia after treatment of the cause should always be confirmed by laboratory testing (usually 4–6 weeks after correction of the primary disease). If hyperlipidemia has not resolved, wrong diagnosis, ineffective treatment, or concurrent primary or secondary hyperlipidemia of other cause should be considered.

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 hypertriglyceridemia 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 mmol/L (500 mg/dL) (Ford, 1996). Primary hypercholesterolemia is usually associated with less severe complications compared to hypertriglyceridemia. 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,

1996; Johnson, 2005). 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).

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 <5.65 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 safely 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.

References

Aguirre, A., Center, S.A., Randolph, J., Yeager, A., Keegan, A., Harvey, H., Erb, H., 2007. Gallbladder disease in Shetland Sheepdogs: 38 cases (1995–2005). Journal of the American Veterinary Medical Association 231, 79–88.

Anderson, N.V., Low, D.G., 1965. Diseases of the canine pancreas: a comparative summary of 103 cases. Animal Hospital 1, 189–194.

Anderson, N.V., Strafuss, A.C., 1971. Pancreatic disease in dogs and cats. Journal of the American Veterinary Medical Association 159, 885–891.

Armstrong, P.J., Ford, R.B., 1989. Hyperlipidemia. In: Kirk, R.W. (Ed.), Current Veterinary Therapy X. WB Saunders, Philadelphia, Pennsylvania, pp. 1046–1050.

Bailhache, E., Nguyen, P., Krempf, M., Siliart, B., Magot, T., Ouguerram, K., 2003. Lipoproteins abnormalities in obese insulin-resistant dogs. Metabolism: Clinical and Experimental 52, 559–564.

Barrie, J., Watson, T.D.G., Stear, M.J., Nash, A.S., 1993. Plasma cholesterol and lipoprotein concentrations in the dog: the effects of age, breed, gender and endocrine disease. Journal of Small Animal Practice 34, 507–512.

Bass, V.D., Hoffman, W.E., Droner, J.L., 1976. Normal canine lipid profiles and effects of experimentally induced pancreatitis and hepatic necrosis on lipids. American Journal of Veterinary Research 37, 1355–1357.

Bauer, J.E., 1992. Diet-induced alterations of lipoprotein metabolism. Journal of the American Veterinary Medical Association 201, 1691–1694.

Bauer, J.E., 1995. Evaluation and dietary considerations in idiopathic hyperlipidemia in dogs. Journal of the American Veterinary Medical Association 206, 1684–1688.

Bauer, J.E., 1996. Comparative lipid and lipoprotein metabolism. Veterinary Clinical Pathology 25, 49–56.

Bauer, J.E., 2004. Lipoprotein-mediated transport of dietary and synthesized lipids and lipid abnormalities of dogs and cats. Journal of the American Veterinary Medical Association 224, 668–675.

Baum, D., 1969. Congenital lipoprotein lipase deficiency and hyperlipemia in the young puppy. Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine 131, 183–185.

Blomhoff, J.P., Holme, R., Ostrem, T., 1978. Plasma cholesterol esterification and plasma lipoproteins in bile-duct-ligated dogs. Scandinavian Journal of Gastroenterology 13, 693–702.

Bodkin, K., 1992. Seizures associated with hyperlipoproteinemia in a Miniature Schnauzer. Canine Practice 17, 11–15.

Boland, L.L., Folsom, A.R., Rosamond, W.D., 2002. Hyperinsulinemia, dyslipidemia, and obesity as risk factors for hospitalized gallbladder disease: a prospective study. Annals of Epidemiology 12, 131–140.

Burkhard, M.J., Meyer, D.J., 1995. Causes and effects of interference with clinical laboratory measurements and examinations. In: Bonagura, J.D. (Ed.), Kirk's Current Veterinary Therapy XII. WB Saunders, Philadelphia, Pennsylvania, pp. 14–20.

Cameron, J.L., Capuzzi, D.M., Zuidema, G.D., Margolis, S., 1974. Acute pancreatitis with hyperlipemia. Evidence for a persistent defect in lipid metabolism. American Journal of Medicine 56, 482–487.

Center, S.A., Smith, C.A., Wilkinson, E., Erb, H.N., Lewis, R.M., 1987. Clinicopathological, renal immunofluorescent, and light microscopic features of glomerulonephritis in the dog – 41 Cases (1975–1985). Journal of the American Veterinary Medical Association 190, 81–90.

Center, S.A., 1996. Hepatic lipidosis, glucocorticoid hepatopathy, vacuolar hepatopathy, storage disorders, amyloidosis, and iron toxicity. In: Strombeck, D.R., Guilford, W.G., Center, S.A., Williams, D.A., Meyer, D.J. (Eds.), Strombeck's Small Animal Gastroenterology. WB Saunders, Philadelphia, Pennsylvania, pp. 766–801.

Chikamune, T., Katamoto, H., Ohashi, F., Shimada, Y., 1995. Serum lipid and lipoprotein concentrations in obese dogs. Journal of Veterinary Medical Science 57, 595–598.

Chikamune, T., Katamoto, H., Nomura, K., Ohashi, F., 1998. Lipoprotein profile in canine pancreatitis induced with oleic acid. Journal of Veterinary Medical Science 60, 413–421.

Chuang, J.H., Shieh, C.S., Chang, N.K., Chen, W.J., Lo, S.K., 1995. Metabolic effect of parenteral nutrition in dogs with obstructive jaundice. Journal of the American College of Nutrition 14, 197–201.

Connelly, P.W., 1999. The role of hepatic lipase in lipoprotein metabolism. Clinica Chimica Acta 286, 243–255.

Cook, A.K., Breitschwerdt, E.B., Levine, J.F., Bunch, S.E., Linn, L.O., 1993. Risk factors associated with acute pancreatitis in dogs: 101 cases (1985–1990). Journal of the American Veterinary Medical Association 203, 673–679.

Cook, A.K., Cowgill, L.D., 1996. Clinical and pathological features of protein-losing glomerular disease in the dog: a review of 137 cases (1985–1992). Journal of the American Animal Hospital Association 32, 313–322.

Crispin, S.M., 1993. Ocular manifestations of hyperlipoproteinemia. Journal of Small Animal Practice 34, 500–506.

Danielsson, B., Ekman, R., Johansson, B.G., Petersson, B.G., 1977. Plasma lipoprotein changes in experimental cholestasis in dog. Clinica Chimica Acta 80, 157–170.

Deckelbaum, R.J., Eisenberg, S., Oschry, Y., Butbul, E., Sharon, I., Olivecrona, T., 1982. Reversible modification of human plasma low-density lipoproteins toward triglyceride-rich precursors – a mechanism for losing excess cholesterol esters. Journal of Biological Chemistry 257, 6509–6517.

Dibartola, S.P., Tarr, M.J., Parker, A.T., Powers, J.D., Pultz, J.A., 1989. Clinicopathologic findings in dogs with renal amyloidosis – 59 cases (1976–1986). Journal of the American Veterinary Medical Association 195, 358–364.

Dibartola, S.P., Tarr, M.J., Webb, D.M., Giger, U., 1990. Familial renal amyloidosis in Chinese Shar-Pei dogs. Journal of the American Veterinary Medical Association 197, 483–487.

Diez, M., Michaux, C., Jeusette, I., Baldwin, P., Istasse, L., Biourge, V., 2004. Evolution of blood parameters during weight loss in experimental obese Beagle dogs. Journal of Animal Physiology and Animal Nutrition 88, 166–171.

Dixon, R.M., Reid, S.W., Mooney, C.T., 1999. Epidemiological, clinical, haematological and biochemical characteristics of canine hypothyroidism. Veterinary Record 145, 481–487.

Downs, L.G., Crispin, S.M., Legrand-defretin, V., PerezCamargo, G., McCappin, T., Bolton, C.H., 1997. The effect of dietary changes on plasma lipids and lipoproteins of six Labrador Retrievers. Research in Veterinary Science 63, 175–181.

Elliott, D.A., 2005. Dietary and medical considerations in hyperlipidemia. In: Ettinger, S.J., Feldman, E.C. (Eds.), Textbook of Veterinary Internal Medicine. Saunders Elsevier, St. Louis, Missouri, pp. 592–595.

Feldman, E.C., Nelson, R.W., 2004. Canine and Feline Endocrinology and Reproduction. Saunders, St. Louis, Missouri. pp. 85–645.

Ford, R.B., 1993. Idiopathic hyperchylomicronemia in Miniature Schnauzers. Journal of Small Animal Practice 34, 488–492.

Fielding, C.J., Fielding, P.E., 1995. Molecular physiology of reverse cholesterol transport. Journal of Lipid Research 36, 211–228.

Ford, R.B., 1996. Clinical management of lipemic patients. Compendium on Continuing Education for the Practicing Veterinarian 18, 1053–1060.

Fortson, M.R., Freedman, S.N., Paul, D., 1995. Clinical assessment of hyperlipidemic pancreatitis. American Journal of Gastroenterology 90, 2134–2139.

Froyland, L., Asiedu, D.K., Vaagenes, H., Garras, A., Lie, O., Totland, G.K., Berge, R.K., 1995. Tetradecylthioacetic acid incorporated into very low density lipoprotein: changes in the fatty acid composition and reduced plasma lipids in cholesterol-fed hamsters. Journal of Lipid Research 36, 2529–2540.

Ginsberg, H.N., 1998. Lipoprotein physiology. Endocrinology and Metabolism Clinics of North America 27, 503–519.

Gleeson, J.M., Hejazi, J.S., Kwong, L., Chan, I.F., Le, T., Alberts, A.W., Wilson, D.E., 1990. Plasma apolipoprotein-E, high-density lipoprotein-1 (Hdl1) and urinary mevalonate excretion in pancreatectomized diabetic dogs – effects of insulin and lovastatin. Atherosclerosis 84, 1–12.

Goodhead, B., 1971. Importance of nutrition in the pathogenesis of experimental pancreatitis in the dog. Archives of Surgery 103, 724–727.

Guyton, A.C., Hall, J.E., 2000. Digestion and absorption in the gastrointestinal tract. In: Guyton, A.C., Hall, J.E. (Eds.), Textbook of Medical Physiology. WB Saunders, Philadelphia, Pennsylvania, pp. 754–763.

Havel, R.J., 1969. Pathogenesis, differentiation and management of hypertriglyceridemia. Advances in Internal Medicine 15, 117–154.

Hess, R.S., Saunders, H.M., Van Winkle, T.J., Shofer, F.S., Washabau, R.J., 1998. Clinical, clinicopathologic, radiographic, and ultrasonographic abnormalities in dogs with fatal acute pancreatitis: 70 cases (1986–1995). Journal of the American Veterinary Medical Association 213, 665–670.

Hess, R.S., Kass, P.H., Shofer, F.S., Van Winkle, T.J., Washabau, R.J., 1999. Evaluation of risk factors for fatal acute pancreatitis in dogs. Journal of the American Veterinary Medical Association 214, 46–51.

Hess, R.S., Saunders, H.M., Van Winkle, T.J., Ward, C.R., 2000. Concurrent disorders in dogs with diabetes mellitus: 221 cases (1993–1998). Journal of the American Veterinary Medical Association 217, 1166–1173.

Hess, R.S., Kass, P.H., Van Winkle, T.J., 2003. Association between diabetes mellitus, hypothyroidism or hyperadrenocorticism, and atherosclerosis in dogs. Journal of Veterinary Internal Medicine 17, 489–494.

Huang, H.P., Yang, H.L., Liang, S.L., Lien, Y.H., Chen, K.Y., 1999. Iatrogenic hyperadrenocorticism in 28 dogs. Journal of the American Animal Hospital Association 35, 200–207.

Hubert, B., Braun, J.P., de la Farge, F., Mangol, J.P., 1987. Hypertriglyceridemia in two related dogs. Companion Animal Practice 1, 33–35.

Illingworth, D.R., Connor, W.E., Hatcher, L.F., Harris, W.S., 1989. Hypolipemic effects of $n-3$ fatty-acids in primary hyperlipoproteinemia. Journal of Internal Medicine 225, 91–97.

Jeusette, I., Grauwels, M., Cuvelier, C., Tonglet, C., Istasse, L., Diez, M., 2004. Hypercholesterolaemia in a family of rough collie dogs. Journal of Small Animal Practice 45, 319–324.

Jeusette, I.C., Lhoest, E.T., Istasse, L.P., Diez, M.O., 2005. Influence of obesity on plasma lipid and lipoprotein concentrations in dogs. American Journal of Veterinary Research 66, 81–86.

Johnson, M.C., 2005. Hyperlipidemia disorders in dogs. Compendium on Continuing Education for the Practicing Veterinarian 27, 361–364.

Jonas, A., 2000. Lecithin cholesterol acyltransferase. Biochimica et Biophysica Acta 1529, 245–256.

Kagawa, Y., Hirayama, K., Uchida, E., Izumisawa, Y., Yamaguchi, M., Kotani, T., Niiyama, M., Yoshino, T., Taniyama, H., 1998. Systemic atherosclerosis in dogs: histopathological and immunohistochemical studies of atherosclerotic lesions. Journal of Comparative Pathology 118, 195–206.

Kashyap, M.L., McGovern, M.E., Berra, K., Guyton, J.R., Kwiterovich, P.O., Harper, W.L., Toth, P.D., Favrot, L.K., Kerzner, B., Nash, S.D., Bays, H.E., Simmons, P.D., 2002. Long-term safety and efficacy of a once-daily niacin/lovastatin formulation for patients with dyslipidemia. American Journal of Cardiology 89, 672–678.

LeBlanc, C.J., Bauer, J.E., Hosgood, G., Mauldin, G.E., 2005. Effect of dietary fish oil and vitamin E supplementation on hematologic and serum biochemical analytes and oxidative status in young dogs. Veterinary Therapeutics 6, 325–340.

Lindsay, S., Entenmann, C., Chaikoff, I.L., 1948. Pancreatitis accompanying hepatic disease in dogs fed a high fat, low protein diet. A.M.A. Archives of Pathology 45, 635–638.

Ling, G.V., Stabenfeldt, G.H., Comer, K.M., Gribble, D.H., Schechter, R.D., 1979. Canine hyperadrenocorticism: pretreatment clinical and laboratory evaluation of 117 cases. Journal of the American Veterinary Medical Association 174, 1211–1215.

Littman, M.P., Dambach, D.M., Vaden, S.L., Giger, U., 2000. Familial protein-losing enteropathy and protein-losing nephropathy in Soft Coated Wheaten Terriers: 222 cases (1983–1997). Journal of Veterinary Internal Medicine 14, 68–80.

Liu, S.K., Tilley, L.P., Tappe, J.P., Fox, P.R., 1986. Clinical and pathological findings in dogs with atherosclerosis – 21 cases (1970–1983). Journal of the American Veterinary Medical Association 189, 227–232.

Logas, D., Beale, K.M., Bauer, J.E., 1991. Potential clinical benefits of dietary supplementation with marine-life oil. Journal of the American Veterinary Medical Association 199, 1631–1636.

Mahley, R.W., Weisgraber, K.H., 1974. Canine lipoproteins and atherosclerosis. I. Isolation and characterization of plasma lipoproteins from control dogs. Circulation Research 35, 713–721.

Mahley, R.W., Weisgraber, K.H., Innerarity, T., 1974. Canine lipoproteins and atherosclerosis. II. Characterization of plasma lipoproteins associated with atherogenic and nonatherogenic hyperlipidemia. Circulation Research 35, 722–733.

Mahley, R.W., Innerarity, T.L., Weisgraber, K.H., Fry, D.L., 1977. Canine hyperlipoproteinemia and atherosclerosis: accumulation of lipid by aortic medial cells in-vivo and in-vitro. American Journal of Pathology 87, 205–225.

Maldonado, E.N., Romero, J.R., Ochoa, B., Aveldano, M.I., 2001. Lipid and fatty acid composition of canine lipoproteins. Comparative Biochemistry and Physiology B –Biochemistry and Molecular Biology 128, 719–729.

Nelson, R.W., Turnwald, G.H., Willard, M.D., 2004. Endocrine, metabolic, and lipid disorders. In: Willard, M.D., Tvedten, H. (Eds.), Small Animal Clinical Diagnosis by Laboratory Methods. Saunders St. Louis, Missouri, pp. 165–207.

Nieto, C.G., Barrera, R., Habela, M.A., Navarrete, I., Molina, C., Jimenez, A., Serrera, J.L., 1992. Changes in the plasma concentrations of lipids and lipoprotein fractions in dogs infected with *Leishmania infantum*. Veterinary Parasitology 44, 175–182.

Ogilvie, G.K., Ford, R.B., Vail, D.M., Walters, L.M., Salman, M.D., Babineau, C., Fettman, M.J., 1994. Alterations in lipoprotein profiles in dogs with lymphoma. Journal of Veterinary Internal Medicine 8, 62–66.

Panciera, D.L., 1994. Hypothyroidism in dogs: 66 cases (1987–1992). Journal of the American Veterinary Medical Association 204, 761–767.

Pike, F.S., Berg, J., King, N.W., Penninck, D.G., Webster, C.R.L., 2004. Gallbladder mucocele in dogs: 30 cases (2000–2002). Journal of the American Veterinary Medical Association 224, 1615–1622.

Rifai, N., Bachorik, P.S., Albers, J.J., 1999. Lipids, lipoproteins, and apolipoproteins. In: Burtis, C.A., Ashwood, E.R. (Eds.), Tietz Textbook of Clinical Chemistry. WB Saunders, Philadelphia, Pennsylvania, pp. 809–861.

Rogers, W.A., Donovan, E.F., Kociba, G.J., 1975a. Idiopathic hyperlipoproteinemia in dogs. Journal of the American Veterinary Medical Association 166, 1087–1091.

Rogers, W.A., Donovan, E.F., Kociba, G.J., 1975b. Lipids and lipoproteins in normal dogs and in dogs with secondary hyperlipoproteinemia. Journal of the American Veterinary Medical Association 166, 1092–1100.

Rogers, W.A., 1977. Lipemia in the dog. Veterinary Clinics of North America Small Animal Practice 7, 637–647.

Saharia, P., Margolis, S., Zuidema, G.D., Cameron, J.L., 1977. Acute pancreatitis with hyperlipidemia: studies with an isolated perfused canine pancreas. Surgery 82, 60–67.

Sato, K., Agoh, H., Kaneshige, T., Hikasa, W., Kagota, K., 2000. Hypercholesterolemia in Shetland Sheepdogs. Journal of Veterinary Medical Science 62, 1297–1301.

Schenck, P.A., Donovan, D., Refsal, K.N.R., Rick, M., 2004. Incidence of hypothyroidism in dogs with chronic hyperlipidemia. Journal of Veterinary Internal Medicine 18, 442.

Scherk, M.A., Center, S.A., 2005. Toxic, metabolic, infectious, and neoplastic liver diseases. In: Ettinger, S.J., Feldman, E.C. (Eds.), Textbook of Veterinary Internal Medicine. Saunders Elsevier, St. Louis, Missouri, pp. 1464–1478.

Schickel, R., 2005. Identification of the nucleotide sequence of the lipoprotein lipase gene as well as its role in the development of hyperlipidemia and pancreatitis in the Miniature Schnauzer. (Dissertation). Ludwig-Maximilians University, Munich, Germany.

Speck, L., 1865. Fall von lipamia. Arch Verin Wissenschaftl Heilkunde. Quoted in: Lipidoses, diseases of the intracellular lipid metabolism. In: Trannhauser, S.J. (Ed.), Grune and Stratton, New York, 1958, p. 307.

Spencer, C.M., Barradell, L.B., 1996. Gemfibrozil – a reappraisal of its pharmacological properties and place in the management of dyslipidaemia. Drugs 51, 982–1018.

Stalenhoef, A.F.H., de Graaf, J., Wittekoek, M.E., Bredie, S.J.H., Demacker, P.N.M., Kastelein, J.J.P., 2000. The effect of concentrated $n-3$ fatty acids versus gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertrygliceridemia. Atherosclerosis 153, 129–138.

Steiner, J.M., 2000. Canine digestive lipases (Dissertation). Texas A&M University, Texas.

Tidholm, A., Jonsson, L., 1997. A retrospective study of canine dilated cardiomyopathy (189 cases). Journal of the American Animal Hospital Association 33, 544–550.

Toskes, P.P., 1990. Hyperlipidemic Pancreatitis. Gastroenterology Clinics of North America 19, 783–791.

Tsutsumi, K., Hagi, A., Inoue, Y., 2001. The relationship between plasma high density lipoprotein cholesterol levels and cholesteryl ester transfer protein activity in six species of healthy experimental animals. Biological and Pharmaceutical Bulletin 24, 579–581.

Vitale, C.L., Olby, N.J., 2007. Neurologic dysfunction in hypothyroid, hyperlipidemic Labrador Retrievers. Journal of Veterinary Internal Medicine 21, 1316–1322.

Wada, M., Minamisono, T., Ehrhart, L.A., Naito, H.K., Mise, J., 1977. Familial hyperlipoproteinemia in Beagles. Life Sciences 20, 999–1008.

Walli, A.K., Seidel, D., 1984. Role of lipoprotein-X in the pathogenesis of cholestatic hypercholesterolemia: uptake of lipoprotein-X and its effect on 3-hydroxy-3-methylglutaryl co-enzyme-A reductase and chylomicron remnant removal in human fibroblasts, lymphocytes, and in the rat. Journal of Clinical Investigation 74, 867–879.

Wang, C.S., Hartsuck, J., 1992. Structure and functional properties of lipoprotein lipase. Biochimica et Biophysica Acta 1123, 1–17.

Watson, P., Simpson, K.W., Bedford, P.G.C., 1993. Hypercholesterolaemia in Briards in the United Kingdom. Research in Veterinary Science 54, 80–85.

Watson, T.D.G., Barrie, J., 1993. Lipoprotein metabolism and hyperlipemia in the dog and cat – a review. Journal of Small Animal Practice 34, 479–487.

Whitney, M.S., Boon, G.D., Rebar, A.H., Ford, R.B., 1987. Effects of acute pancreatitis on circulating lipids in dogs. American Journal of Veterinary Research 48, 1492–1497.

Whitney, M.S., 1992. Evaluation of hyperlipidemias in dogs and cats. Seminars in Veterinary Medicine and Surgery (Small Animal) 7, 292–300.

Whitney, M.S., Boon, G.D., Rebar, A.H., Story, J.A., Bottoms, G.D., 1993. Ultracentrifugal and electrophoretic characteristics of the plasma lipoproteins of Miniature Schnauzer dogs with idiopathic hyperlipoproteinemia. Journal of Veterinary Internal Medicine 7, 253–260.

Williams, D.A., 1996. The Pancreas. In: Strombeck, D.R., Guilford, W.G., Center, S.A., Williams, D.A., Meyer, D.J. (Eds.), Strombeck's Small Animal Gastroenterology. WB Saunders, Philadelphia, Pennsylvania, pp. 381–410.

Williams, D.A., Steiner, J.M., 2005. Canine pancreatic disease. In: Ettinger, S.J., Feldman, E.C. (Eds.), Textbook of Veterinary Internal Medicine. Saunders Elsevier, St. Louis, Missouri, pp. 1482–1488.

Wilson, D.E., Chan, I.F., Elstad, N.L., Pericgolia, L., Hejazi, J., Albu, D.S., Cutfield, R., 1986. Apolipoprotein E-containing lipoproteins and lipoprotein remnants in experimental canine diabetes. Diabetes 35, 933–942.

Xenoulis, P.G., Suchodolski, J.S., Ruaux, C.G., Swim, E.S., Steiner, J.M., 2006. Association between serum triglyceride and canine pancreatic lipase immunoreactivity (cPLI) concentrations in Miniature Schnauzers. Journal of Veterinary Internal Medicine 20, 750 (abstract).

Xenoulis, P.G., Suchodolski, J.S., Levinski, M.D., Steiner, J.M., 2007. Investigation of hypertriglyceridemia in healthy Miniature Schnauzers. Journal of Veterinary Internal Medicine 21, 1224–1230.

Xenoulis, P.G., Suchodolski, J.S., Levinski, M.D., Steiner, J.M., 2008. Serum liver enzyme activities in healthy Miniature Schnauzers with and without hypertriglyceridemia. Journal of the American Veterinary Medical Association 232, 63–67.

Yadav, D., Pitchumoni, C.S., 2003. Issues in hyperlipidemic pancreatitis. Journal of Clinical Gastroenterology 36, 54–62.

Yilmaz, Z., Senturk, S., 2007. Characterization of lipid profiles in dogs with parvoviral enteritis. Journal of Small Animal Practice 48, 643–650. doi:10.1111/j.1748-5827.2007.00391.x.

Zafross, M.K., Dubielzig, R.R., 2007. Solid intraocular xanthogranuloma in three Miniature Schnauzer dogs. Veterinary Ophthalmology 10, 304–307.