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# Diagnostic approach to the hyperlipidemic cat and dietary treatment





**ABBREVIATIONS USED IN THIS CHAPTER**

**ACAT**: acyl-coenzyme A cholesterol acyltransferase
**ALT**: alanine aminotransferase
**AST**: aspartate aminotransferase
**CETP**: cholesteryl ester transfer protein
**DHA**: docosahexaenoic acid
**EPA**: eicosapentaenoic acid
**HDL**: high density lipoproteins
**HMGCoA reductase**: 3-hydroxy-3-methylglutaryl coenzyme A reductase
**IDL**: intermediate density lipoproteins
**LCAT**: lecithin cholesterol acyltransferase
**LDH**: lactate deshydrogenase
**LDL**: low density lipoproteins
**LPL**: lipoprotein lipase
**ME**: metabolizable energy
**VLDL**: very low density lipoproteins

# Diagnostic approach to the hyperlipidemic cat and dietary treatment

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Hyperlipidemia *or* hyperlipemia *refers to an abnormally high lipid concentration in serum or plasma. Normally hyperlipidemia occurs after ingesting a meal, especially a meal high in fat, but fasting hyperlipidemia is indicative of abnormal lipid metabolism. (The term lipemia, the presence of lipids in serum or plasma, is often incorrectly used to describe an abnormal excess concentration of circulating lipids).*

Hyperlipidemia *and* hyperlipoproteinemia *are often used interchangeably, but hyperlipoproteinemia more correctly refers to an excess of circulating lipoproteins.*

Hypercholesterolemia *and* hypertriglyceridemia *refer respectively to an abnormally high concentration of circulating cholesterol or triglyceride. They both may occur alone or in combination with hyperlipoproteinemia.*

# 1 - Lipid metabolism

Perturbations in any aspect of lipid metabolism may result in abnormal hyperlipidemia. Abnormalities may occur in:
- lipid absorption, synthesis, esterification
- lipoprotein synthesis, receptor-mediated uptake
- bile formation and circulation or reverse cholesterol transport.

## ► Lipid absorption

Cholesterol and triglycerides are absorbed in the small intestine. Cholesterol may be ingested in the diet (exogenous), or is derived from biliary secretion and desquamation of intestinal epithelial cells (endogenous) which may account for up to 50% of the total cholesterol present in the small intestinal lumen *(Holt, 1972)*.

Absorption requires bile acids and micelle formation. Salts of bile acids are secreted by the liver and enter the small intestine via the bile, and most secreted salts exist as conjugates with taurine in cats. When the concentration of bile salts reaches a high enough level, bile salts form aggregates or micelles *(Feldman et al, 1983)*, and allow approximately 30 to 60% of available cholesterol to be absorbed. Within the lumen of the intestine, cholesteryl esters from micelles are hydrolysed by pancreatic cholesterol esterase. Free cholesterol passively diffuses across the intestinal mucosal cell wall *(Westergaard & Dietschy, 1976)*. Within the intestinal cell, free cholesterol is re-esterified with fatty acids, and is mediated by the enzyme acyl CoA: cholesterylacyltransferase (ACAT). A combination of free cholesterol and cholesteryl esters are then secreted into chylomicron particles.

Within the intestinal lumen, triglycerides are hydrolysed by pancreatic lipase to monoglycerides, diglycerides, and free fatty acids **(Figure 1)**. In combination with cholesterol, phospholipid, and bile salts, these monoglycerides, diglycerides, and free fatty acids form mixed micelles. These micelles release monoglycerides, diglycerides, and free fatty acids at the intestinal cell wall where they are absorbed. Within the intestinal cell, monoglycerides and diglycerides are re-esterified to form triglycerides. Triglycerides along with cholesteryl esters, free cholesterol, phospholipid, and proteins will be incorporated into chylomicron particles for release into the circulation via the lymphatic system by way of the thoracic duct.

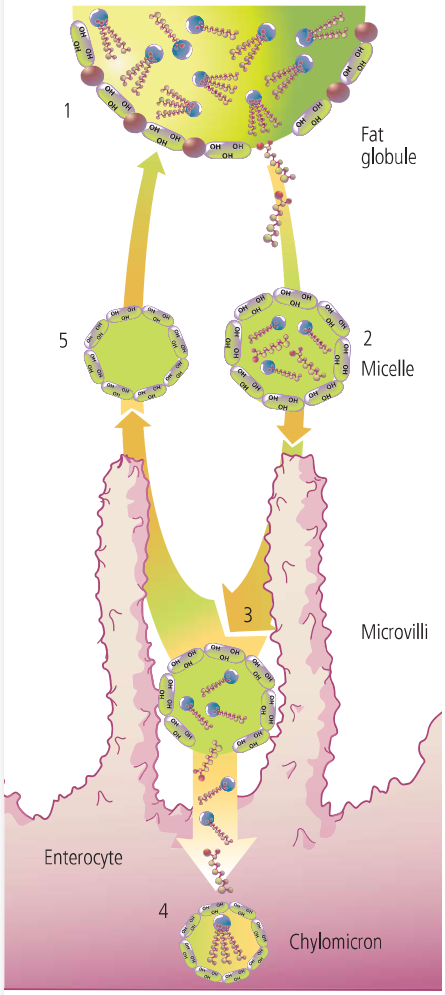
## ► Cholesterol synthesis

Endogenous cholesterol synthesis contributes to the total body cholesterol concentration. Cholesterol can be synthesized by almost all cells, with the highest rate of synthesis in the liver and intestine *(Turley & Dietschy, 1981)*. In humans, approximately 1 g cholesterol per day is synthesized within the body from acetyl CoA, and the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCoA reductase) is the rate-limiting enzyme in cholesterol synthesis *(Alberts, 1988)*.

## ► Lipoprotein production

Lipoproteins are the main carriers of cholesterol in the blood and are important in the delivery of cholesterol to all tissues. Circulating lipoproteins are classified by their size, density, and electrophoretic behavior *(Mahley & Weisgraber, 1974)*. Lipoproteins in humans have been well characterized *(Alaupovic et al, 1968; Assmann, 1982; Shepherd & Packard, 1989)*, but direct correlations cannot be made to the feline due to many differences in lipoprotein characteristics *(Mahley et al, 1974; Mahley & Weisgraber, 1974)*.

**FIGURE 1 - DIGESTION AND ABSORPTION OF LIPIDS**
*(From Gogny, 1994)*




*1- Fat globules: lipases act on the surface of the emulsion*

*2- Micelle: transport form for fatty acids*

*3- Fat release to the enterocytes*

*4- Triglycerides resynthesis and incorporation in chylomicrons*

*5- Absorption of biliary salts in the ileum*

Lipoproteins are micellar particles with a hydrophobic core containing triglycerides and cholesteryl esters, and an amphipathic outer surface containing phospholipid, unesterified cholesterol, and proteins *(Assmann, 1982)*. Proteins within a lipoprotein tend to be specific for that lipoprotein class. Lipoprotein particles are not static, but are in a dynamic state of equilibrium, with transfer of components occurring between lipoproteins.

Five major classes of lipoproteins have been characterized, including:

- **chylomicrons**
- **very low density lipoproteins (VLDL)**
- **intermediate density lipoproteins (IDL)**
- **low density lipoproteins (LDL)**
- **and high density lipoproteins (HDL).**

Some mammals (humans and most monkeys) have a predominance of LDL and are classified as "LDL mammals" *(Chapman, 1986)*. LDL mammals are more sensitive to elevations in LDL cholesterol and the development of atherosclerosis. Cats and most other mammals are considered "HDL mammals" due to the predominance of circulating HDL. HDL mammals are less sensitive to elevated LDL cholesterol concentrations, and are more resistant to the development of atherosclerosis **(Table 1)**.

**TABLE 1 - PREDOMINANCE OF CERTAIN LIPOPROTEINS BY SPECIES**

| "LDL mammals" | "HDL mammals" |
|---|---|
| Humans and most Monkeys | Dogs |
| Rabbits | Cats |
| Hamsters | Horses |
| Guinea pigs | Ruminants |
| Pigs | Rats |
| Camels | Mice |
| Rhinoceros | Most other mammals |

*LDL: Low Density Lipoproteins*
*HDL: High Density Lipoproteins*

## ► Chylomicrons

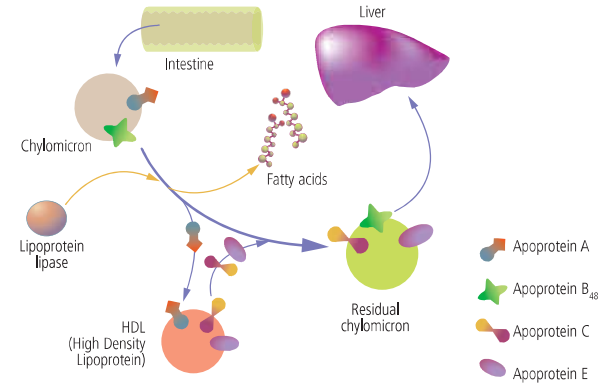
Chylomicrons are the largest of the lipoproteins with the lowest density **(Table 2)**. Chylomicrons have a high triglyceride content, low protein content and remain at the origin on lipoprotein electrophoresis *(Bauer, 1996)*. Chylomicrons contain different types of apoproteins. In the peripheral circulation, chylomicrons contribute apoprotein A to HDL in exchange for apoprotein C and E **(Figure 2)**, increasing their protein content *(Capurso, 1987)*. A chylomicron remnant is formed.

Lipoprotein lipase (LPL) activated by apoprotein C-II of chylomicrons hydrolyzes the triglyceride present in chylomicrons, creating a phos-

**TABLE 2 - FELINE LIPOPROTEIN CHARACTERISTICS**

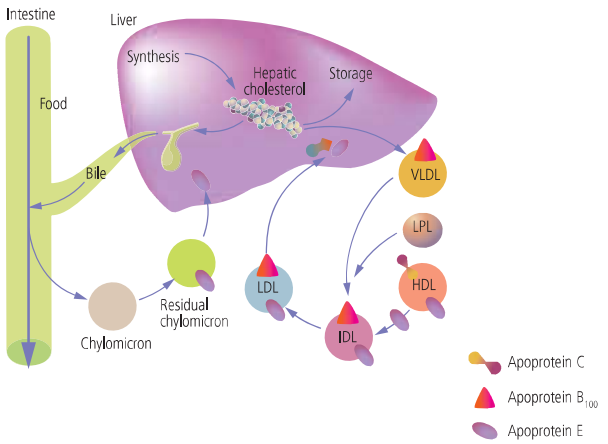
| | | | APPROXIMATE COMPOSITION (%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Lipoproteins** | **Hydrated density g/mL** | **Electrophoretic mobility** | **Triglycerides** | **Cholesteryl ester** | **Free cholesterol** | **Proteins** | **Phospholipids** | **Major apoproteins** |
| Chylomicrons | 0.960 | Origin | **90** | 2 | 1 | 2 | 6 | $B_{48}$ |
| VLDL | < 1.006 | β (pre-β) | **60** | 13 | 7 | 5 | 15 | $B_{100}$, E, C |
| LDL | 1.030 – 1.043 | β | 10 | **38** | 8 | 22 | 22 | $B_{100}$ |
| HDL<br>- HDL2<br>- HDL3 | -<br>1.063 – 1.100<br>1.100 – 1.210 | -<br>α1<br>α1 | 4<br>-<br>- | 16<br>-<br>- | 6<br>-<br>- | 50<br>-<br>- | 25<br>-<br>- | -<br>E, A-1, C<br>A, C |

**FIGURE 2 - CHYLOMICRON METABOLISM**




*Chylomicron particles containing a high concentration of triglyceride are released from the intestinal mucosal cell into the lymphatics and to the circulation. Lipoprotein lipase hydrolysis of triglycerides within chylomicrons releases fatty acids and decreases the triglyceride content of chylomicrons, creating a chylomicron remnant. In addition, there is an exchange of apoproteins between HDL and chylomicrons. Chylomicrons contribute apoprotein A to HDL in exchange for apoproteins C and E. The chylomicron remnant formed is recognized by an apoprotein E receptor on hepatocytes and is removed from the circulation. A deficiency of lipoprotein lipase activity can result in decreased metabolism of chylomicrons to chylomicron remnants and thus a prolonged appearance of chylomicrons in the circulation.*

**FIGURE 3 - CHYLOMICRON, VLDL, LDL, AND LIVER CHOLESTEROL METABOLISM**




*Chylomicron particles containing lipids are released from the intestine into the circulation. Cholesterol-rich chylomicron remnants form and are recognized by the apoprotein E receptor on hepatocytes. Once in the hepatocyte, cholesterol can be stored as cholesteryl ester (via the action of ACAT), can be excreted into bile as cholesterol or bile acids, or secreted into VLDL particles. Synthesis of cholesterol in the hepatocyte (via HMGCoA reductase) contributes to the available cholesterol pool. Lipoprotein lipase hydrolysis of triglyceride within secreted VLDL and exchange of apoproteins create a triglyceride-depleted IDL which forms the triglyceride-poor, cholesterol-enriched LDL particle. The LDL receptor recognizes apoproteins B and E and mediates uptake and removal of LDL from the circulation. A deficiency of lipoprotein lipase activity can result in decreased metabolism of VLDL to LDL and thus a prolonged appearance of VLDL in the circulation.*

pholipid-rich particle. Lipoprotein lipase is associated with endothelial cell surfaces, interacting with membrane associated heparan sulfate *(Nilsson-Ehle et al, 1980)*. Chylomicron remnant formation is necessary for hepatic clearance of chylomicrons *(Cooper, 1977)*. Once chylomicron remnants are formed, they are rapidly removed from the circulation by the apoprotein E receptor in liver cells *(Mahley et al, 1989)*.

## ► Very low density lipoproteins (VLDL)

VLDL are synthesized by hepatocytes **(Figure 3)**, and are a major transporter of triglyceride *(Mills & Taylaur, 1971)*. VLDL are smaller and heavier than chylomicrons, have a density of < 1.006 g/mL, and contain apoproteins B100, E, and C. VLDL binds to LPL, and LPL hydrolyzes the triglyceride present in VLDL. This process may create VLDL remnants which can be removed by the liver via receptor or non-receptor-mediated uptake *(Havel, 1984)*. Feline VLDL exhibits pre-β migration on lipoprotein electrophoresis, which is similar to human VLDL.

## ► Low density lipoproteins (LDL)

HDL transfers apoprotein E to VLDL, creating an IDL particle. With further loss of triglyceride, phospholipid, and apoprotein, LDL is formed. Removal of LDL from the circulation is via the LDL receptor which binds both apoprotein B and apoprotein E *(Goldstein & Brown, 1984)*. Feline

LDL exhibits β migration on lipoprotein electrophoresis, have a density of 1.030 - 1.043 g/mL, and contain apoprotein B100.

## ► High density lipoproteins (HDL)

HDL are the smallest and heaviest of the lipoproteins, with the greatest quantity of protein and least quantity of triglyceride of any of the lipoproteins. Cats have approximately 5 times more HDL than LDL unlike humans, but similar to the canine. Feline HDL is divided into 2 subclasses based on composition and density:

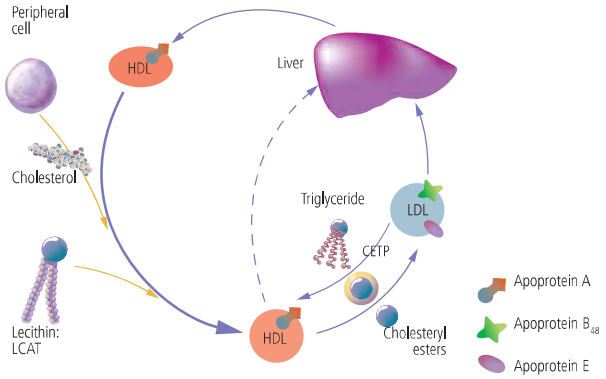
- HDL2 has a density of 1.063 – 1.100 g/mL, and contains apoproteins E, A-1, and C.
- HDL3 is smaller than HDL2 with a density of 1.100 – 1.210 g/mL, and contains apoproteins A and C.

Both HDL2 and HDL3 exhibit α1-migration on lipoprotein electrophoresis *(Demacker et al, 1987)*.

Nascent HDL is secreted by the liver **(Figure 4)**, and contains very little free cholesterol and cholesteryl ester. Free cholesterol is transferred from peripheral cells to nascent HDL, and these cholesterol-rich particles serve as substrate for lecithin cholesterol acyltransferase (LCAT), converting free cholesterol to cholesteryl esters. With the increased concentration of cholesteryl esters, the core of HDL enlarges and becomes more spherical. Hepatic lipase may also play a role in the interconversion of HDL subfractions *(Groot et al, 1981)*. The conversion of free cholesterol to cholesteryl esters and its subsequent transfer to other lipoproteins allows additional free cholesterol to transfer from the surface of cells and other lipoproteins to HDL *(Kostner et al, 1987)*. Thus LCAT plays a key role in the transfer of free cholesterol from peripheral tissues to the liver *(Albers et al, 1986)*.

In humans, cholesteryl ester transfer protein (CETP) is responsible for cholesteryl ester and triglyceride exchange between HDL and LDL or VLDL. Cholesteryl ester derived from free cholesterol in peripheral cells is transferred to LDL, which can then return to the liver via receptor-mediated uptake (reverse cholesterol transport) *(Noel et al, 1984)*. This mechanism for returning peripheral cholesterol to the liver has been termed reverse cholesterol transport. Cats however have low levels of CETP *(Guyard-Dangremont et al, 1998)*, and thus there is little transfer of cholesteryl ester to LDL. Without cholesteryl ester transfer, HDL remains enriched with cholesteryl esters, and is designated HDL1, or HDLc. In the cat, reverse cholesterol transport is completed via HDL uptake by the liver. The cat is a "HDL mammal" since most of the circulating cholesterol is carried by HDL and cannot be transferred to LDL as in humans (a "LDL mammal").

**FIGURE 4 - REVERSE CHOLESTEROL TRANSPORT**




*Discoidal HDL (nascent HDL) is secreted by the liver and obtains unesterified cholesterol from peripheral cells. LCAT in the circulation esterifies this cholesterol, resulting in a more spherical cholesteryl ester-rich particle. If cholesteryl ester transfer protein (CETP) is present, cholesteryl ester is transferred from HDL to LDL, with exchange of triglyceride from LDL to HDL. LDL carrying cholesteryl ester derived from peripheral cells returns to the liver completing reverse cholesterol transport. In dogs with little CETP, other mechanisms exist to return cholesterol to the liver via HDL directly.*

# 2 - Diagnostic approach to the hyperlipidemic patient

When a patient exhibits serum hyperlipidemia after a 10 to 12 hour fast **(Figure 5)**, investigation into the cause is warranted **(Figure 6)**. The presumption that the cat was fasted should be verified, to ensure that all access to food has been withheld. Once fasting hyperlipidemia has been confirmed, the causes of hyperlipidemia secondary to other disorders should be ruled out. If no secondary disorder resulting in hyperlipidemia is evident, then a primary hyperlipidemia should be considered.

## ► Serum turbidity

Visual evaluation of the degree of serum turbidity can provide an estimation of serum triglyceride concentration:

- normal, clear serum: typical triglyceride concentration < 200 mg/dL (2.3 mmol/L)
- hazy serum: triglyceride concentration around 300 mg/dL (3.4 mmol/L)
- opacity of the serum: triglyceride concentration approaches 600 mg/dL (6.8 mmol/L)
- serum with the appearance of skim milk: triglyceride concentration is usually around 1000 mg/dL (11.3 mmol/L)
- serum with the appearance of whole milk: triglyceride concentration as high as 2500 (28.2 mmol/L) to 4000 mg/dL (45.2 mmol/L)

## ► Refrigeration test

To ascertain the lipoprotein classes that may be present in excess, a simple refrigeration test can be performed **(Figure 7)**. The serum sample is refrigerated and left undisturbed overnight. Chylomicrons, being the least dense lipoprotein, will "float" forming a "cream layer" on the top of the serum sample *(Rogers, 1977)*. If the serum below the chylomicron layer is clear, then only

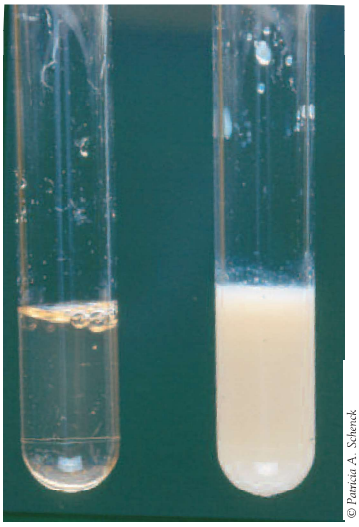



***Figure 5 - The appearance of normal and hyperlipidemic serum.*** *Normal serum should be clear, with no evidence of turbidity (left tube). Fasting serum that is turbid indicates the presence of excess lipid in the serum (right tube).*


***Figure 7 - Refrigeration test of hyperlipidemic serum.*** *On the left, a fasting serum sample shows hyperlipidemia. After the refrigeration test, there is the appearance of a lactescent layer ("cream layer") floating on top of the serum. This layer is due to increased chylomicron particles present in the serum sample. Note that the serum below the top lactescent layer is also turbid, indicating the presence of other lipoproteins in excess (in addition to the excess chylomicron particles).*

**FIGURE 6 - ALGORITHM TO DETERMINE THE CAUSE OF HYPERLIPIDEMIA**

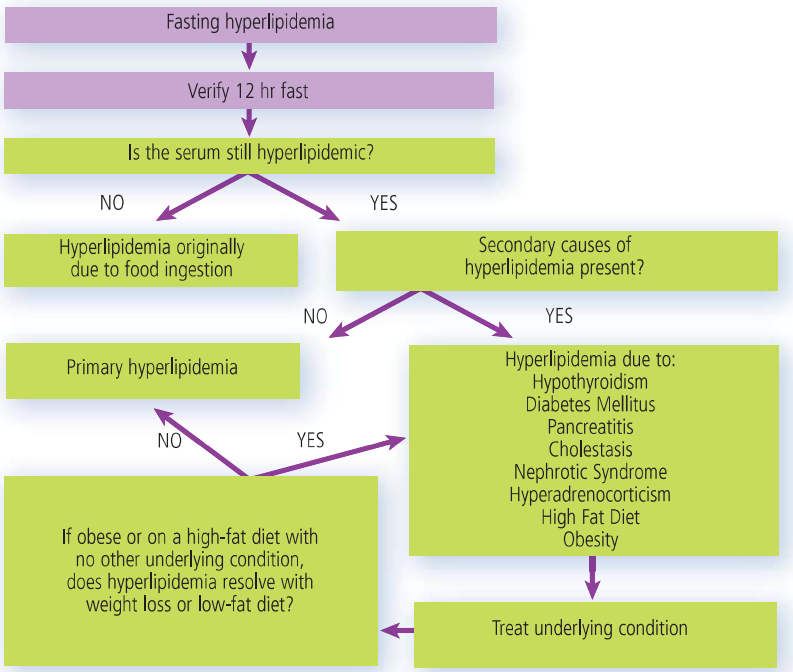
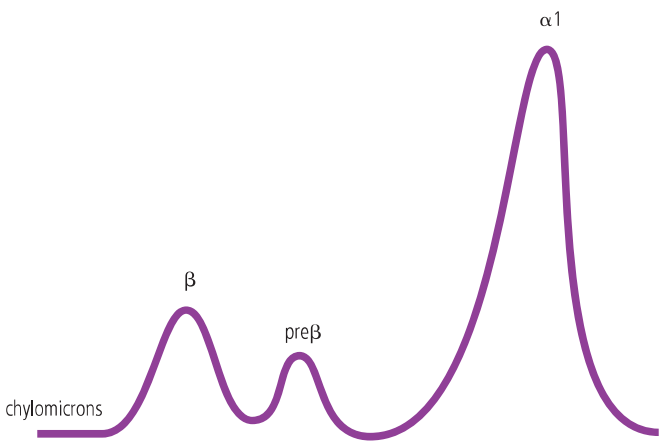


**FIGURE 8 - DENSITOMETRIC TRACING OF A LIPOPROTEIN ELECTROPHORETOGRAM FROM A NORMAL CAT.**




*The peaks from left to right represent the relative concentrations of β-migrating lipoproteins (LDL), preβ-migrating lipoproteins (VLDL), and α1-migrating lipoproteins (HDL2/HDL3). Note the predominance of α1-migrating lipoproteins in the normal cat (a HDL mammal). A small percentage of chylomicrons may be present in normal cats; chylomicrons will exhibit a small peak at the origin if present.*

chylomicrons are present in excess, and either a non-fasted sample, or primary hyperchylomicronemia should be suspected. If the serum below the chylomicron layer is turbid, then other lipoproteins are present in excess in addition to the hyperchylomicronemia. If a "cream layer" does not form after refrigeration, then chylomicrons are not present, and the visible hyperlipidemia is due to an excess of other lipoproteins.

## ► Lipoprotein electrophoresis

Lipoprotein electrophoresis can be used to characterize lipoproteins in serum. With electrophoresis, lipoproteins separate based on their charge and mobility on agarose gel. The agarose gel is then stained and scanned using a densitometer to semi-quantify classes of lipoproteins **(Figure 8)**. Lipoprotein electrophoresis should be performed on fresh, not-previously-frozen serum, and the scan interpreted by someone knowledgeable of feline lipoprotein characteristics (i.e. not a human laboratory), since differences exist between humans and cats in electrophoretic pattern. Lipoprotein electrophoresis is not quantitative, but is useful to identify an excess in a particular lipoprotein class.

## ► Ultracentrifugation

Ultracentrifugation can be utilized to separate lipoproteins based on density. Ultracentrifugation is time-consuming, requires expensive equipment, and considerable skill to produce reliable results. Thus ultracentrifugation is rarely available except in the research setting.

## ► Serum interferences

Excess of other analytes present in serum may interfere with the measurement of lipids:
- hyperbilirubinemia may cause a false lowering of cholesterol measurement
- if cholesterol is present at a concentration of greater than 700 mg/dL, the measured triglyceride concentration may be falsely lowered *(Shephard & Whiting, 1990)*
- hypertriglyceridemia may result in a falsely lower cholesterol concentration *(Cobbaert & Tricarico, 1993)*
- pentobarbital may falsely increase triglyceride measurement *(Hata et al, 1978)*, but phenobarbitone has no effect on cholesterol concentration *(Foster et al, 2000)*.

Depending on the methodology utilized for analysis, hyperlipidemia may interfere with a number of assays. Hyperlipidemia may result in an approximately 2% increase in sodium, urea, glucose, chloride, and total protein measurement *(Miyada et al, 1982)*. Total calcium measurement may be slightly elevated *(Darras et al, 1992)*, and cortisol may be slightly elevated, but not clinically significant *(Lucena et al, 1998)*. Bilirubin concentration may be falsely increased *(Ng et al, 2001)*, and immunoglobulin A, immunoglobulin M, haptoglobin and α1-antitrypsin concentration may also be falsely increased *(Bossuyt & Blanckaert, 1999)*. Concentration of LDH is decreased and AST and ALT concentrations are increased *(Miyada et al, 1982)*. Hypertriglyceridemia may interfere with WBC, RBC, hemoglobin and platelet measurements *(Peng et al, 2001)*, and causes a false increase in haptoglobin concentration *(Weidmeyer & Solter, 1996)*. Glycated hemoglobin measurement may be falsely decreased *(Garrib et al, 2003)*, and free thyroxine measured by ELISA may be increased *(Lucena et al, 1998)*. However, triglyceride concentration up to 10mg/dL will not interfere with phenobarbital measurement *(Baer & Paulson, 1987)*.

# 3 - Causes of hyperlipidemia

Hyperlipidemia may be the result of lipid abnormalities secondary to other conditions, or may be a primary disorder of lipid metabolism **(Table 3)**. In the cat, recognized primary disorders include inherited hyperchylomicronemia, and idiopathic hypercholesterolemia. Conditions that can result in secondary hyperlipidemia include hypothyroidism, pancreatitis, diabetes mellitus, nephrotic syndrome, hyperadrenocorticism, cholestasis, obesity or the feeding of very high fat diets.

**TABLE 3 - CAUSES OF HYPERLIPIDEMIA IN THE CAT**

| |
|---|
| **Postprandial** |
| **Primary**<br>Inherited hyperchylomicronemia<br>Idiopathic hypercholesterolemia |
| **Secondary**<br>Hypothyroidism<br>Pancreatitis<br>Diabetes Mellitus<br>Nephrotic Syndrome<br>Hyperadrenocorticism<br>Cholestasis<br>Obesity<br>"High fat" diets |

## ► Hypothyroidism

Naturally occurring hypothyroidism is rare in cats, and may be congenital or acquired. Iatrogenically-induced hypothyroidism is more common in the cat, arising from treatment for hyperthyroidism. Increases in both serum cholesterol and triglyceride concentrations have been associated with canine hypothyroidism *(Boretti et al, 2003; Rogers et al, 1975)*, and cholesterol elevations are usually moderate *(Jaggy et al, 1994)*. Both serum cholesterol and triglyceride concentrations return to normal with adequate thyroid replacement therapy *(Rogers et al, 1975)*. Changes in lipoproteins have not been evaluated in hypothyroid cats.

In humans with hypothyroidism, mRNA for LDL receptors is decreased resulting in decreased cholesterol and chylomicron clearance *(Kovanen, 1987)*. Lipoprotein lipase activity may be altered *(Hansson et al, 1983; Pykalisto et al, 1976)*, and there is decreased excretion of cholesterol into bile *(Gebhard & Prigge, 1992)*. Cholesterol synthesis is also decreased, but the decrease in clearance is greater than the decrease in synthesis, leading to a net increase in cholesterol concentration *(Field et al, 1986)*.

Naturally occurring atherosclerosis has been noted in dogs with hypothyroidism *(Manning, 1979)*, but has not been observed in the cat.

## ► Pancreatitis

In humans, there is evidence that pancreatitis is associated with decreased LPL activity *(Hazzard et al, 1984)*. This decreased activity of LPL may result in increased triglyceride concentrations with slower clearance of chylomicrons. Two dogs with pancreatitis also exhibited a moderate decrease in LPL activity, which returned to normal with treatment and resolution of the pancreatitis *(Schenck, unpublished observations)*.

In cats, pancreatitis usually results in hyperlipidemia with elevations in serum cholesterol *(Hill & Van Winkle, 1993)* and possibly triglyceride concentrations. Pancreatitis can be a cause of hyperlipidemia, or a sequel to hyperlipidemia. Little is known regarding lipoprotein abnormalities in the cat with pancreatitis.

## ► Diabetes mellitus

In diabetes mellitus, elevations of both serum triglyceride and cholesterol concentrations are typically observed *(Rogers et al, 1975)*. Lipoproteins have not been characterized in the diabetic cat, but abnormalities have been well characterized in humans.

In humans with diabetes mellitus, LPL activity is decreased, with an increase in free fatty acids *(Steiner et al, 1975)* and hepatic lipase activity *(Muller et al, 1985)*. Urinary mevalonate concentration is elevated approximately six-fold, indicating an increase in whole-body cholesterol synthesis, and HMGCoA reductase activity is increased in both the liver and intestine *(Feingold et al, 1994; Kwong et al, 1991)*. There is impaired removal of VLDL from the circulation *(Wilson et al, 1986)*, and a decrease in the number and affinity of LDL receptors *(Takeuchi, 1991)*. Prolonged retention of lipoprotein

*Since cats and humans both typically exhibit Type 2 diabetes mellitus characterized by insulin resistance, it is likely that there are lipoprotein similarities.*

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remnants may contribute to an increased delivery of cholesterol to extrahepatic tissues, and the increased concentration of HDL1 reflects a disturbance in cholesterol transport from peripheral cells back to the liver *(Wilson et al, 1986)*.

Naturally occurring atherosclerosis has been observed at necropsy in a dog with diabetes mellitus *(Sottiaux, 1999)*, but this has not yet been noted in the diabetic cat.

## ► Nephrotic syndrome

Lipoprotein abnormalities have not been characterized in cats with nephrotic syndrome. Cats with nephrotic syndrome may exhibit mild elevations in serum cholesterol and triglyceride.

Lipoprotein abnormalities in nephrotic syndrome and chronic renal disease have been well characterized in humans, and the progression of renal dysfunction has been shown to correlate with serum total cholesterol *(Washio et al, 1996)*. Lipoprotein lipase activity is decreased which may account for the hypertriglyceridemia due to a decrease in lipoprotein clearance *(Olbricht, 1991)*. There is decreased clearance of LDL *(Shapiro, 1991; Vaziri & Liang, 1996)* due to decreased LDL receptor expression *(Portman et al, 1992)*. LDL may also be increased due to an increase in synthesis *(de Sain-van der Velden et al, 1998)*. HMGCoA reductase activity is increased in the liver *(Chmielewski et al, 2003; Szolkiewicz et al, 2002)*, and the increased cholesterol does not up-regulate LDL receptors *(Liang & Vaziri, 1997)*. Reverse cholesterol transport is impaired *(Kes et al, 2002)*, and ACAT activity within the liver is increased with a decrease in LCAT activity *(Liang & Vaziri, 2002)*.

VLDL increases due to decreased catabolism *(de Sain-van der Velden et al, 1998)*, and proteinuria may also stimulate VLDL synthesis by the liver, induced by hypoalbuminemia *(D'Amico, 1991)*. Impaired clearance of VLDL may be due to deficiencies in apoprotein C-II, apoprotein C-III, and apoprotein E, creating smaller VLDL particles that are not cleared efficiently by receptors *(Deighan et al, 2000)*. This altered structure of VLDL results in altered binding to endothelial bound LPL *(Shearer & Kaysen, 2001)*, and proteinuria may also be associated with the urinary loss of heparan sulfate, an important cofactor for LPL *(Kaysen et al, 1986)*. Synthesis of apoprotein A-I by the liver increases in response to proteinuria *(Marsh, 1996)*, and protein catabolism in peripheral tissues is increased.

## ► Hyperadrenocorticism

Hyperadrenocorticism is uncommon in the cat. In cats with hyperadrenocorticism, hypercholesterolemia may be noted *(Moore et al, 2000)*. Hypercholesterolemia may be more prevalent in cases of pituitary-dependent hyperadrenocorticism than in hyperadrenocorticism caused by adrenal tumors. Many cats with hyperadrenocorticism also have concurrent diabetes mellitus which can also cause an increase in serum cholesterol and other lipid abnormalities. In dogs with hyperadrenocorticism, concentrations of both VLDL and LDL have been noted, but lipoproteins have not been characterized in cats with hyperadrenocorticism.

Lipoprotein lipase activity may be decreased with an increase in hepatic lipase activity *(Berg et al, 1990)*. In addition, hypercortisolism stimulates production of VLDL by the liver *(Taskinen et al, 1983)*. Excess glucocorticoids stimulate lipolysis, and this excess fat breakdown exceeds the liver's capacity for clearance. The occurrence of steroid hepatopathy in hyperadrenocorticism may lead to biliary stasis resulting in further lipid abnormalities.

## ► Cholestasis

In cats with induced cholestasis, hypercholesterolemia was observed *(Center et al, 1983)*. There may be alterations in the content of lipoproteins *(Danielsson et al, 1977)*, but changes in lipoproteins have not been characterized in cats with cholestasis. Hepatic lipidosis arising from weight

loss may cause cholestasis through accumulation of excess triglyceride in hepatocytes. Hepatic lipidosis results in an increase in triglyceride, VLDL, and LDL *(Blanchard et al, 2004)*. LDL becomes enriched with triglyceride, and HDL is enriched with cholesterol suggesting that VLDL secretion is enhanced and VLDL/LDL catabolism is decreased.

### ► Obesity

In 10 obese cats, serum concentrations of triglyceride and cholesterol were significantly increased with an increase in triglyceride content of VLDL as compared to lean cats *(Hoenig et al, 2003)*. There was no significant difference in serum non-esterified fatty acids or phospholipids, and ultracentrifugation revealed no differences in density of lipoproteins. Lower LPL activity has been observed in obese cats *(Hoenig et al, 2006)* as has been observed in obese dogs *(Schenck, unpublished data)*. Weight loss decreases serum triglyceride and cholesterol concentrations, with a decrease in LDL and VLDL *(Fettman et al, 1998)*. In another study, obese cats also showed a decreased serum cholesterol concentration, but no decrease in LDL with weight loss *(Dimski et al, 1992)*.

### ► High fat diets

The feeding of high fat diets may result in hyperlipidemia and moderate elevation in serum triglycerides and cholesterol concentrations *(Ginzinger et al, 1997; Thiess et al, 2004)*. HDL-cholesterol, LDL-cholesterol, and triglyceride concentrations were statistically elevated in cats fed a diet containing 30% fat, 3% cholesterol (as fed) for 2 to 8 months *(Ginzinger et al, 1997)*. Changes in lipoprotein migration on electrophoresis have not been characterized in the cat. It is also unknown at what level of dietary fat that cholesterol and triglyceride changes may be noted in the absence of additional dietary cholesterol.



## 4 - Primary hyperlipidemia

Once it is verified that hyperlipidemia occurs after a 10- to 12-hour fast, and all possible causes of secondary hyperlipidemia have been ruled out, a presumptive diagnosis of primary hyperlipidemia is made. There is one well described heritable primary hyperlipidemia in cats. In humans, many different gene mutations or defects resulting in primary hyperlipidemias have been characterized. It is likely that with further study and characterization, additional defects causing primary hyperlipidemia will be identified in the cat.

An idiopathic familial hyperchylomicronemia was first reported in two cats in New Zealand *(Jones et al, 1983)*. Since that time, inherited hyperchylomicronemia has been reported in cats in a number of countries including the USA *(Bauer & Verlander, 1984; Grieshaber et al, 1991)*, France *(Jones, 1993)*, and the UK *(Watson et al, 1992)*. The fact that many of the cats in these initial studies were related, suggested an inherited condition.

*Idiopathic familial hyperchylomicronemia is often recognized in kittens or young cats, and affects a number of different breeds.*

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**TABLE 4 - PHYSICAL EXAMINATION FINDINGS AND CLINICAL SIGNS ASSOCIATED WITH HYPERLIPIDEMIA IN CATS**

| |
|---|
| Cutaneous xanthomata (most common) |
| *Lipemia retinalis* (most common) |
| Lipid keratopathy |
| Peripheral nerve paralysis |
| Horner's syndrome |
| Tibial nerve paralysis |
| Radial nerve paralysis |
| Splenomegaly |
| Decreased body fat mass |
| Failure to grow |
| *Weakness (less common)* |
| *Lethargy (less common)* |



***Figure 9 - Xanthomata in a hyperlipidemic cat.*** *Xanthomata are often present in peripheral nerves and can cause a Horner's syndrome.*



***Figure 10 - Blood appearance in case of hyperchylomicronemia.*** *With inherited hyperchylomicronemia, there are marked elevations in serum triglyceride and cholesterol, and blood will often have a "creamy tomato soup" appearance.*

The most common physical examination findings of inherited hyperchylomicronemia are xanthomata and *lipemia retinalis* **(Table 4)** *(Jones, 1993)*.

**Xanthomata** are lipid deposits in skin and organs **(Figure 9)**. Xanthomata are often present in peripheral nerves *(Jones et al, 1986)*, and Horner's syndrome, tibial nerve paralysis, and radial nerve paralysis are most common. Xanthomata can also occur in the liver, spleen, lymph nodes, kidney, heart, muscle, and intestines *(Thompson et al, 1989; Johnstone et al, 1990; Grieshaber et al, 1991; Chanut et al, 2005)*. The histopathology of these lesions have been studied, and are characterized by abnormal lipid accumulation in tissues *(Thompson et al, 1989)*.

*Lipemia retinalis* occurs when hypertriglyceridemia is severe and greater than 15 mmol/L (1364 mg/dl). Lipid keratopathy *(Carrington, 1983)*, lipid in the anterior chamber of the eye *(Brooks, 1989)*, or lipid deposition at the limbus have also been noted in some cats. Weakness, lethargy, and failure to grow have been noted, and affected animals have a higher incidence of being stillborn.

With inherited hyperchylomicronemia, there are marked elevations in serum triglyceride and cholesterol, and blood will often have a 'cream tomato soup' appearance **(Figure 10)**. In one study, the mean cholesterol concentration in 24 cats with inherited hyperchylomicronemia was 6.6 mmol/L (reference range 1.1-5.0 mmol/L) (255 mg/dL; range 42-193 mg/dL), and the mean triglyceride concentration was 10.02 mmol/L (reference range 0.2-0.6 mmol/L) (888 mg/dL; reference range 18-53 mg/dL).

Serum concentration of triglyceride can be extremely elevated in some cats, with triglyceride concentrations reported near 147 mmol/L (13,000 mg/dL) *(Bauer & Verlander, 1984)*. The condition is characterized by a great excess of chylomicrons *(Bauer & Verlander, 1984)*, or by excess chylomicrons with slight increase in VLDL *(Jones et al, 1986)*. This condition most closely resembles Type I hyperlipidemia in humans. Atherosclerosis has not been noted in cats with inherited hyperchylomicronemia despite the lipoprotein abnormalities *(Johnstone et al, 1990)*.

Lipoprotein lipase activity is virtually absent in the inherited hyperchylomicronemia caused by a Gly412Arg missense mutation of the LPL gene of cats. The decrease in LPL activity is not due to a lack of apoprotein C-II which is necessary for LPL activation *(Watson et al, 1992)*. *Peritz et al* (1990) report that the LPL mass is normal in affected cats, but speculate the LPL protein is abnormal and cannot bind to endothelium. However, *Ginzinger et al* (1996) reported an absence of circulating mass of LPL but did find mutant mRNA forms in tissues. A similar defect of LPL has been noted in mink with severe hyperchylomicronemia, normal LPL mass, but no LPL activity *(Christophersen et al, 1997)*.

The cause of hyperchylomicronemia has been shown to be a mutation in the LPL gene *(Ginzinger et al, 1996)*, and both homozygotes and heterozygotes for LPL deficiency have been described *(Ginzinger et al, 1999)*. Homozygotes tend to be more severely affected than heterozygotes, and the severity of hyperchylomicronemia and hypertriglyceridemia is dependent on the magnitude of decrease in LPL activity. In a brother to a severely affected kitten, hypertriglyceridemia was observed but not of the same magnitude as in the severely affected kitten, and LPL activity was decreased but not to the same degree *(Bauer & Verlander, 1984)*.

Adult cats that are homozygous for LPL deficiency have a significantly decreased body fat mass as compared to those that are clinically normal or heterozygotes for LPL deficiency *(Backus et al, 2001)*. Homozygotes born to homozygote dams had a significantly lower body fat mass than homozygotes born to heterozygote dams. Thus the body fat mass depends not only on the lipoprotein status of the cat, but also on the LPL status of the dam.

Another condition that has characteristics similar to inherited hyperchylomicronemia has been observed *(Gunn-Moore et al, 1997)*. Transient hyperlipidemia and anemia has been noted in litters

of kittens with marked increase in chylomicrons and moderate increase in VLDL. After resolution of hyperlipidemia with the feeding of diets containing 9% fat as-fed (approximately 28 g fat/1000 kcal), LPL activity was only mildly lower in affected kittens as compared to normal kittens. These kittens did not exhibit the LPL gene mutation that has been shown in the inherited hyperchylomicronemia that has been well characterized. This suggests the presence of a separate distinct primary hyperlipidemia.

# 5 - Effects of persistent hyperlipidemia

Long-term effects of hyperlipidemia in cats are unknown. Cats are resistant to the development of atherosclerosis compared to humans, due to differences in lipoprotein metabolism between the species. Experimental atherosclerosis has been induced in cats by feeding a diet containing 30% fat, 3% cholesterol (as fed) for 2 to 8 months *(Ginzinger et al, 1997)*.

## ► Atherosclerosis

Atherosclerosis is a specific type of arteriosclerosis with deposition of lipid and cholesterol in the arterial tunica intima and tunica media *(Liu et al, 1986)*. It is unclear however, whether cats with inherited hyperchylomicronemia are at increased risk for the development of atherosclerosis. Studies of lipoprotein interactions with arterial walls have shown that large lipoprotein molecules such as chylomicrons and VLDL have a low influx into the intima *(Nordestgaard et al, 1992)*. Thus inherited hyperchylomicronemia may not be associated with premature atherosclerosis *(Ebara et al, 2001)*.

An increased incidence of atherosclerosis has been noted in association with causes of secondary hyperlipidemia in dogs and humans, but has not been reported in cats. This may be due to the low incidence of some causes of secondary hyperlipidemia in the cat, such as hypothyroidism where there has been evidence for associated atherosclerosis in the dog.

## ► Pancreatitis

There is evidence that persistent hyperlipidemia may lead to pancreatitis *(Dominguez-Munoz et al, 1991)*, and pancreatitis often occurs in humans with inherited hyperchylomicronemia and LPL deficiency. A burst of free radical activity in pancreatic acinar cells disrupts glutathione homeostasis and may be the initiating event in pancreatitis *(Guyan et al, 1990)*. Increased free radical activity may relate to pancreatic ischemia resulting from sluggish pancreatic microcirculation due to high concentrations of chylomicrons *(Sanfey et al, 1984)*. Free radical damage causes leakage of lipase into pancreatic microcirculation. Lipase causes hydrolysis of triglyceride present in excess chylomicrons or VLDL resulting in release of free fatty acids which are intensely inflammatory. Free fatty acids can also cause activation of Hageman factor, or may bind calcium leading to microthrombi and capillary damage. Phospholipid present in chylomicrons and VLDL are also susceptible to free radical attack leading to lipid peroxidation, intensifying inflammation. This results in an increase in release of pancreatic lipase and further lipolysis, leading to pancreatitis *(Havel, 1969)*.

## ► Diabetes mellitus

Persistent hyperlipidemia may also cause diabetes mellitus *(Sane & Taskinen, 1993)*, and diabetes mellitus has been noted as a sequel to inherited hyperchylomicronemia in humans. Increased triglyceride and free fatty acids may lead to insulin resistance due to inhibition of glucose oxidation and glycogen synthesis *(Boden, 1997)*. Free fatty acids may stimulate glyconeogenesis which contributes to inappropriate glucose production *(Rebrin et al, 1995)*. Increased free fatty acids early on act to stimulate insulin production even with low glucose concentrations. In the long term, increased free fatty acids modulate, β-cell gene expression and inhibit insulin secretion *(Prentki &*

*Corkey, 1996)*. By multiple mechanisms, increased serum triglyceride and free fatty acids can lead to hyperglycemia and diabetes mellitus. If hyperlipidemia is corrected, diabetes mellitus caused by hyperlipidemia can be reversed *(Mingrone et al, 1999)*.

# 6 - Treatment of hyperlipidemia

Because of the clinical signs associated with primary hyperlipidemia, and the potential risks, hyperlipidemia should be treated aggressively in the cat. The underlying disorder in a secondary hyperlipidemia should be treated, but there is no specific therapeutic regimen for cats with inherited hyperchylomicronemia.

## ► Fat restricted-diet

The main therapy of primary hyperlipidemia involves feeding a low-fat diet with moderate protein content. Diets low in protein may cause an increase in serum cholesterol concentration (*Hansen et al, 1992*), and are therefore not recommended unless the presence of other conditions warrant their use. Human patients with inherited hyperchylomicronemia typically must restrict dietary fat intake to less than 15% of calories to control hyperlipidemia.

Feline diets with less than 10% fat (as-fed) or less than 30g fat/1000 kcal are generally adequate. Protein content should be maintained at about 30% as-fed, or greater than 85g protein/1000 kcal. A diet should not be chosen only on the percent fat present in the diet; the diet should be low in fat based on metabolizable energy (ME). Some diets appear low in fat on a percentage basis, but actually provide a higher fat content than expected when the amount of fiber in the diet and metabolizable energy are taken into account. For example, a diet containing 11% fat with an ME of 4000 kcal/kg provides only 27.5 g fat/1000 kcal, whereas a diet containing 9% fat with an ME of 3000 kcal/kg provides 30 g fat/1000 kcal **(Table 5)**. The presence of a blend of fructo-oligosaccharides and beet pulp in the diet may also be desirable, since this blend has been shown to decrease serum triglyceride and cholesterol concentrations in the dog *(Diez et al, 1997)*.

Obesity in association with familial hyperchylomicronemia is uncommon, so it is usually not necessary to restrict caloric intake. If the cat is not obese, the amount of food offered may need to be increased because of the decreased calories provided by the new diet with decreased fat content. Many cats can continue to be fed free-choice. Treats should be restricted since these are most likely not low in fat content.

After feeding a low-fat diet for approximately 4 weeks, the presence of hyperlipidemia should be re-evaluated. Most cats will show at least partial resolution of hyperlipidemia with consumption of low-fat diets. Body condition should be assessed, and if there has been significant weight loss, the patient should receive an increased amount of diet, or possibly be switched to a different diet with higher caloric density.

If after 4 weeks hyperlipidemia is still present, the diet should be continued, and all other sources of food or treats removed. If there has been good owner compliance, then a switch to a different low-fat diet could be considered. The patient should then be reassessed after another one to two months. If hyperlipidemia still persists at that time, drug therapy could be added.

**TABLE 5 - INTERPRETATION OF THE FAT CONTENT IN DIETS**

| | Diet A | Diet B |
|---|---|---|
| **Amount of fat g/100g diet** | 11 | 9 |
| ME kcal/100 g diet | 400 | 300 |
| Fat content | 11 g x 1000 kcal/400kcal = 27.5 g fat/1000 kcal | 9 g x 1000 kcal/400kcal = 30.0 g fat/1000 kcal |

## ► Omega-3 fatty acid supplementation

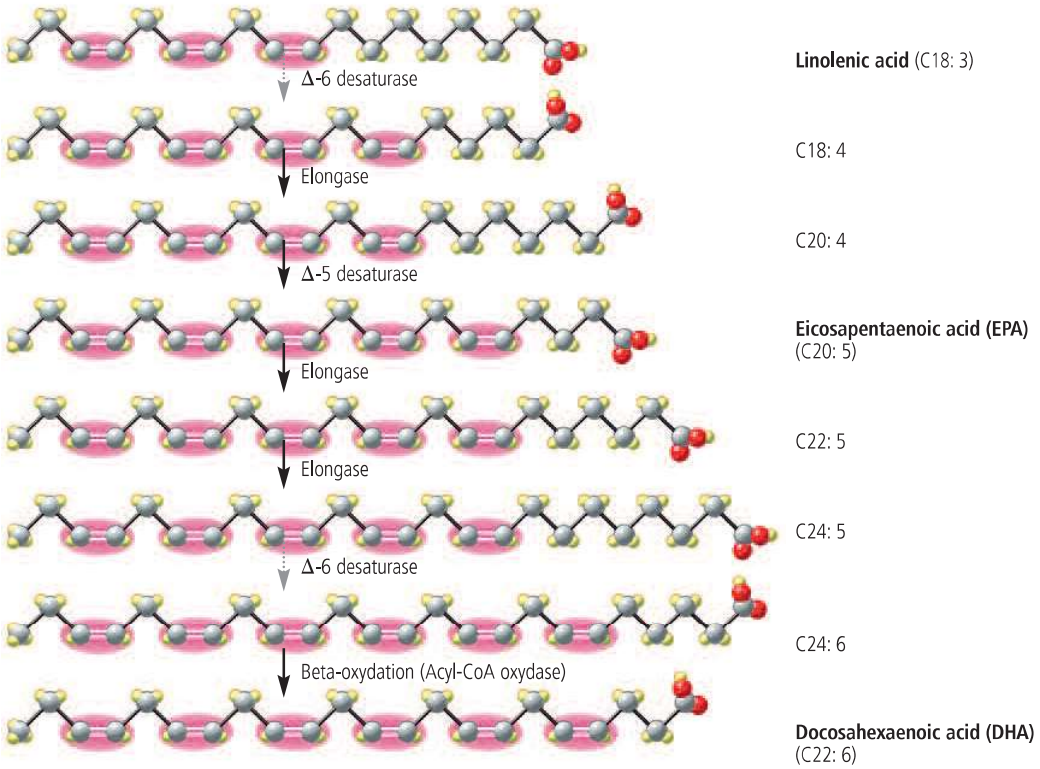
Fish oils are rich in omega-3 fatty acids, and have been the supplement of choice in the treatment of dogs with primary hyperlipidemias. However, little is known about the effectiveness of fish oil therapy in cats. Potential doses range from 10 to 200 mg/kg body weight. The fish oil supplement should contain a high percentage of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as these are long-chain omega-3 fatty acids. Products containing a high level of linolenic acid (also an omega-3 fatty acid) will not be as effective, as cats have very low delta-6 desaturase necessary for the conversion of linolenic acid to longer chain omega-3 fatty acids *(Sinclair et al, 1979)* **(Figure 11)**.

The use of fish oil in the treatment of hyperlipidemia has been extensively studied in a number of other species. Fish oil supplement has resulted in a decrease in serum triglyceride and cholesterol in humans *(Okumura et al, 2002)*, rats *(Adan et al, 1999)*, chicks *(Castillo et al, 2000)*, dogs *(Brown et al, 2000)*, and rabbits *(Mortensen et al, 1998)*.

Omega-3 fatty acids act to decrease the synthesis of triglyceride and VLDL in the liver *(Harris et al, 1990; Connor et al, 1993)*, stimulate LPL activity *(Levy et al, 1993)*, decrease the intestinal absorption of lipid *(Thomson et al, 1993)*, and increase cholesterol secretion into bile *(Smit et al, 1991)*. Fish oil also decreases the serum concentration of free fatty acids *(Singer et al, 1990)*, which may be important in the prevention of pancreatitis and diabetes mellitus.



**FIGURE 11 - METABOLISM OF LINOLENIC ACID (OMEGA-3)**




*Delta-6 desaturase activity is crucial for the efficient production of long-chain omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from available linolenic acid. In the feline, delta-6 desaturase activity is significantly reduced (dotted arrows), and thus there is little production of EPA and DHA from linolenic acid.*

Unfortunately there are no long-term studies to verify the safety and efficacy of any lipid-lowering agent in cats, and any therapy should be used with caution. One concern with fish oil therapy is the evidence that fish oil increases the concentration of lipoperoxides in LDL *(Puiggros et al, 2002)*. The addition of vitamin E to the fish oil therapy regimen may enhance beneficial effects by increasing glutathione reductase activity and decreasing peroxide levels *(Hsu et al, 2001)*.

### ► Other therapeutic agents

Other therapeutic agents have been used with variable results.

- Gemfibrozil has been used to stimulate LPL activity and decrease VLDL secretion *(Santamarina-Fojo & Dugi, 1994)*, and in cats is used at a dosage of 7.5 to 10 mg/kg body weight twice daily.
- Niacin therapy has been used, however adverse effects have been noted *(Bauer, 1995)*.
- Garlic extracts have been used to decrease cholesterol in humans *(Steiner et al, 1996)*, but have not been evaluated in cats.
- HMGCoA reductase inhibitors reduce cholesterol synthesis and increase the excretion of LDL from the circulation, but their effectiveness in cats has not been studied.
- Thyroxine therapy can decrease serum total cholesterol in humans *(Brun et al, 1980)*, and is effective in lowering lipid concentrations in hypothyroid dogs, but its use has not been recommended for cats.

The mutation characterizing the LPL deficiency present in humans and cats with hyperchylomicronemia has been identified, and gene transfer therapy has been attempted. Lipoprotein lipase-deficient cats were given an injection of an adenoviral vector containing the human LPL gene, with disappearance of triglyceride-rich lipoproteins up to day 14, at which time antibodies against the human LPL protein were detected *(Liu et al, 2000)*. Concurrent administration of immunosuppressive therapy delayed antibody production, with resolution of hyperlipidemia for three weeks after administration *(Ross et al, 2006)*. Gene replacement therapy for inherited hyperchylomicronemia may become a reality in the future.

## Conclusion

There are a number of conditions that can cause hyperlipidemia in the feline. Postprandial hyperlipidemia should always be verified, and secondary causes of hyperlipidemia must be ruled out. A number of the causes of secondary hyperlipidemia are uncommon in the cat (hypothyroidism, hyperadrenocorticism), or are fairly evident based on clinical signs or biochemical profile (diabetes mellitus, pancreatitis). If an underlying cause of hyperlipidemia is present, treatment of the primary disease is usually effective at resolving the secondary hyperlipidemia. Primary causes of hyperlipidemia should be aggressively treated because of the potential complications and clinical signs associated with persistent hyperlipidemia.

# Frequently asked questions about feline hyperlipidemia

| Q | A |
|---|---|
| What causes serum to be turbid? | Elevated serum triglyceride carried by lipoproteins causes serum to appear turbid. Opacity is seen when triglyceride concentration approaches 600 mg/dL (6.8 mmol/L). Serum may have the appearance of whole milk when triglyceride concentrations reach 2500 – 4000 mg/dL (28.2-45.2 mmol/L). |
| What conditions cause hyperlipidemia? | The most common cause is a non-fasted animal. If fasting for greater than 12 hours is confirmed, then primary hyperlipidemia, or secondary hyperlipidemia due to hypothyroidism, pancreatitis, diabetes mellitus, hyperadrenocorticism, cholestasis, or nephrotic syndrome may be present. |
| Are high fat diets harmful to cats? | Not usually. Lipid metabolism in cats is very different from that in humans. Cats carry most of their cholesterol in HDL, and are very resistant to the development of atherosclerosis. However, if certain diseases such as hypothyroidism or diabetes mellitus are present, high fat diets could result in further lipid abnormalities. In addition, high fat diets for neutered and sedentary cats can contribute to obesity with subsequent health issues. |
| What causes a "cream layer" to separate in some turbid serum samples? | The "cream layer" which floats to the top of serum is due to the presence of chylomicrons. This is normal in a non-fasted animal, but represents an abnormality if the animal has been fasted for greater than 12 hours. |
| Do cats develop atherosclerosis? | Contrary to humans, cats rarely develop atherosclerosis due to differences in lipid metabolism. Atherosclerosis could develop in some cats that have a concurrent disease that causes chronic hyperlipidemia. |
| Should persistent fasting hyperlipidemia be treated? | Yes. If the hyperlipidemia is due to a secondary cause, then treatment of the underlying condition may resolve the hyperlipidemia. There is evidence suggesting that chronic hyperlipidemia may lead to the development of pancreatitis, insulin resistance, diabetes mellitus, or atherosclerosis in some cats. |

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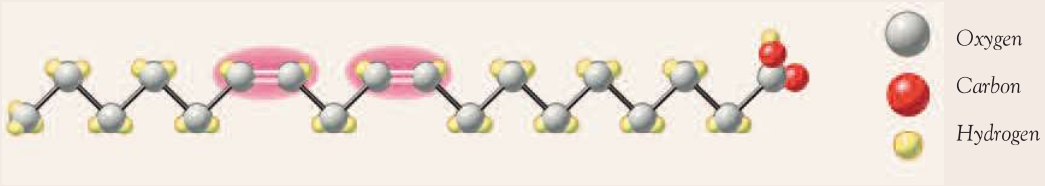
Focus on:

# Long-chain omega-3 fatty acids (EPA-DHA)

Omega-3 fatty acids are a separate family of polyunsaturated fatty acids (PUFA). Their precursor is α-linolenic acid (C18:3, n-3), whose chemical structure distinguishes it from linoleic acid (C18:2, n-6), the precursor of the other main family, omega-6 fatty acids.

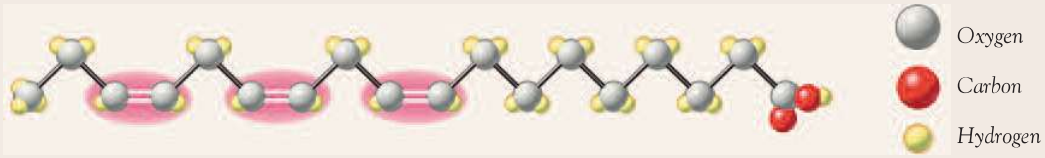
Linoleic acid is an essential fatty acid for cats, which depend on a dietary intake to cover their requirements. With the exception of docosahexaenoic acid (DHA), the omega-3 series of fatty acids are not considered to be essential, as cats can survive with a food that does not contain them. On the other hand, their health may benefit from their introduction in the diet.

**LINOLEIC ACID: C18:2 (N-6); OMEGA-6 FATTY ACID PRECURSOR**




*Omega-6 fatty acids are characterized by the first double bond between the 6th and 7th carbon atom, counting from the omega carbon (the carbon atom located opposite the carboxyl–COOH grouping).*

**α-LINOLENIC ACID: C18:3 (N-3); OMEGA-3 FATTY ACID PRECURSOR**




*In the omega-3 fatty acid family, the first double bond is located between the 3rd and 4th carbon atom.*

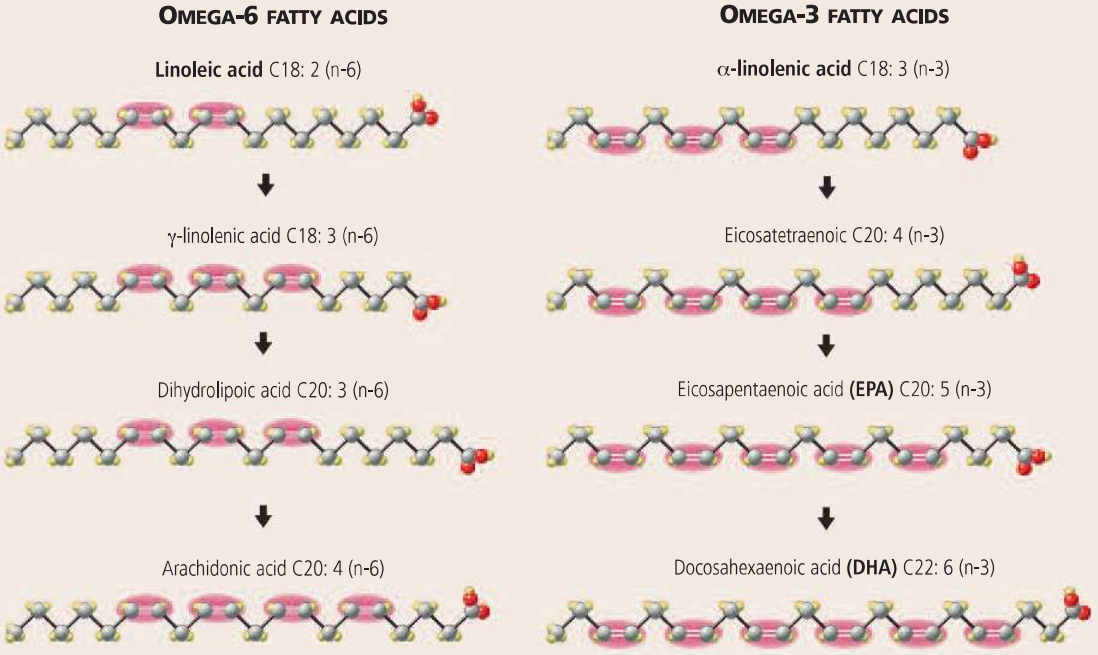
## Metabolism of unsaturated fatty acids

The synthesis of long-chain fatty acids is triggered by the action of enzymes in the liver (desaturase and elongase), which add to the carbon atoms and the unsaturated double bonds. These are the same enzymes that act in the synthesis of omega-3 and omega-6 fatty acids, which explains the competition between the two families.

In cats, the enzyme responsible for the first desaturation, Δ6 desaturase, has a very low-level of activity *(Sinclair et al., 1979; Pawlosky et al., 1994)*.

- In the series of omega-6 fatty acids, Δ6 desaturase produces very low quantities of arachidonic acid. In the absence of dietary intake a healthy adult cat may be able to cover its requirements, but gestating queens will produce no or few viable litters and the proportion of cannibalism appears to be higher *(Morris, 2004)*. Arachidonic acid is therefore deemed essential in cats, contrary to dogs.

**HEPATIC SYNTHESIS OF LONG-CHAIN OMEGA-3 AND OMEGA-6 FATTY ACIDS FROM THEIR RESPECTIVE PRECURSORS**




- With respect to omega-3 fatty acids, the yield from α-linolenic acid (omega-3) is very low. Therefore, when EPA-DHA supplementation is recommended, they should be provided preformed in the food.

## Sources of omega-3 fatty acids

Some vegetable oils, such as soy oil and especially linseed oil, contain a non-negligible quantity of α-linolenic acid. In contrast, oils sourced from the sea are the only useful sources of EPA and DHA.

PUFA sourced from the sea are synthesized in the chloroplasts of phytoplankton or micro-algae consumed by fish. Higher up the food chain, some fish incorporate omega-3 PUFA and their metabolism transforms them until the fatty acids contain 20-22 carbon atoms. EPA and DHA are especially concentrated in the adipose tissue of fish. Fish oils (especially cold sea fish like salmon, mackerel, anchovy, halibut and herring) can contain more than 30% EPA-DHA.

**COMPARATIVE CONTENT OF OMEGA-3 FATTY ACIDS OF DIFFERENT OILS**

| Omega-3 fatty acids (% DM) | Soy oil | Linseed oil | Fish oil |
|---|---|---|---|
| α-linolenic acid | 6 | 51 | <1 |
| EPA + DHA | - | - | 17-34 |



*The adaptation of the cat's metabolism to a carnivorous diet is especially expressed by the specific requirements of essential fatty acids, which differ from those of the dog.*

## Key points
to remember about:

# Nutritional management of hyperlipidemia

1 - **Give the cat a low-fat diet**: < 30 g/1000 kcal or less than 10% fat in a 4000 kcal/kg food:

- in the event of obesity, weight loss is indicated to lower the cholesterol concentration;
- when the body condition is optimal the low-fat diet may need to be supplemented with calories compared with a maintenance food to avoid undesirable weight loss.

2 - When the low-fat diet is inadequate to control hyperlipidemia, fish oil (10-200 mg/kg), which is rich in the long chain omega-3 fatty acids EPA and DHA, can reduce serum lipid concentrations.

3 - Adding a large quantity of unsaturated fatty acids (omega-3) increases the risk of oxidation of the lipid membranes. The administration of biological antioxidants (e.g. vitamin E, vitamin C and beta-carotene) can limit the oxidative reactions.

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