

A literature review on the effects of dietary fatty acids on serum LDL levels and LDL metabolism

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Chapter One Introduction

The Effects of Dietary Fatty Acids on Serum LDL Levels and LDL Metabolism

Dietary saturated fats and *trans*-unsaturated fats are known to cause an increase in serum low density lipoprotein (LDL) concentrations. An increased LDL concentration is a known risk factor for atherosclerosis of the arterial walls leading to coronary heart disease (CHD), stroke, and other cardiovascular diseases. (Schaefer, 2000) About 13 million Americans are estimated to have coronary heart disease with around 450,000 annual deaths attributed to CHD. (American Heart Association [AHA], 2000) Many independent factors are responsible for an individual's risk of elevated LDL and CHD. Diet has proven an important role in prevention and treatment of CHD. Numerous studies have explained how the diet, especially fatty acids, can affect serum LDL levels and LDL metabolism. (Schaefer, 2000) An updated overview of this literature is presented to compare the effects of saturated, *trans*-unsaturated, polyunsaturated, and monounsaturated fatty acids on serum LDL levels and LDL metabolism.

Summary of Established Facts concerning Lipid Metabolism

Rosenson's review of lipoprotein metabolism in 2003 describes exogenous lipid metabolism, which occurs before the production of lipoproteins by the liver and starts with the breaking down of dietary fats into individual fatty acids. (See figure 1, pp. 24) These fatty acids are absorbed through the intestinal mucosa along with dietary cholesterol to be incorporated into chylomicrons, which are specialized lipoproteins for exogenous transport of lipids. (Rosenson) They are usually made up of 85 to 90 percent triglycerides and a small percentage of cholesterol. (Ginsberg & Goldberg, 2002) Chylomicrons are too large to be absorbed into the circulation through the intestinal mucosa, so they are absorbed into the lymphatic system to be transported to the thoracic duct and then into the blood stream. While in the circulation, the triglycerides

become hydrolyzed into free fatty acids by lipoprotein lipase, which can then be utilized by peripheral adipose and muscle cells. The remaining chylomicron remnant, which contains mostly dietary cholesterol, is taken up by the liver to be used for both bile acid formation and excretion, incorporation into membranes, or resecretion as lipoproteins in the circulation. (Ginsberg & Goldberger, 2002; Rosenson, 2003)

Endogenous lipid transport involves two classes of lipoproteins; the Apo B100 lipoprotein system and the Apo AI lipoprotein system. The Apo B100 system transfers lipids from the liver to the peripheral cells and includes low density lipoproteins (LDL), intermediate density lipoproteins (IDL), and very low density lipoproteins (VLDL). The Apo AI system transfers lipids from the peripheral cells back to the liver and includes the high density lipoprotein (HDL). (Ginsberg & Goldberg, 2002; Rosenson, 2003)

The endogenous pathway starts with the synthesis of VLDL by the liver. (See figure 2, pp. 25) VLDL particles consist roughly of about sixty percent triglycerides and twenty percent cholesterol esters. (Rosenson, 2003) Similar to the hydrolysis of chylomicrons, these lipoproteins are also depleted of their triglyceride core. The resulting free fatty acids are utilized by peripheral cells while the VLDL remnants or intermediate density lipoproteins, IDL, are cleared from the circulation by LDL receptors or remnant receptors. The IDLs can also be reconstructed by hepatic lipase to form LDL particles. The smaller and more dense IDLs are more easily converted into LDL, whereas, the larger IDLs consisting of more triglycerides are more likely to be directly removed from the plasma by LDL receptors with the assistance of Apolipoprotein E. (Ginsberg & Goldberg, 2002; Rosenson, 2003)

LDL is a lipoprotein with a smaller percentage of triglyceride than its precursor, VLDL, and contains a core of cholesterol ester. LDL is also enriched with Apo B100, which acts as a

ligand for the LDL to bind to the LDL receptor. (Rosenson, 2003) The fate of LDL can have several directions. LDL can bind to cellular LDL receptors to be utilized for cell membrane synthesis, hormone production, or cholesterol ester storage. It can also be uptaken by hepatocytes to be utilized for bile acid production and excretion into the intestinal lumen for digestion. LDL can also undergo peroxidation which has been shown to induce atherosclerosis, the major cause of CHD. (Ginsberg & Goldberg, 2002; Rosenson, 2003) The oxidized form of LDL will bind to unregulated scavenger receptors on macrophages and endothelial cells of vessels to induce foam cell formation and the secretion of cytokines and growth factors by surrounding cells. This causes the adherence of more monocytes, smooth muscle proliferation and a resulting atheromatous plaque. (Hiltunen et. al., 1998)

LDL receptors play an important role in cholesterol metabolism. Nearly every cell in the body has LDL receptors with most of the circulating LDL being taken up by hepatocytes of the liver. The adrenals have the highest concentration of receptors per cell due to their responsibility of steroid hormone synthesis. LDL receptors are synthesized inside the cell and migrate to regions of the cell membrane where they function to collect LDL or VLDL from the blood stream. (Ginsberg & Goldberg, 2002; Rosenson, 2003) The number of LDL receptors on each cell has been found to be regulated by the amount of cholesterol delivered to the cell by LDL. In the absence of cholesterol, transcription factors called sterol response element regulatory proteins (SREBS) are activated and stimulate LDL receptor gene expression. In addition, with a high accumulation of intracellular cholesterol, LDL receptor synthesis is inhibited by this regulatory process. Intracellular cholesterol production is also regulated by the same process. (Brown, 1986; Ginsberg & Goldberg, 2002.)

The apo A-I lipoprotein system consists of HDL, a lipoprotein that is known for its anti-atherogenic properties. HDL is formed in plasma by fusion of phospholipid and apolipoprotein complexes. (Ginsberg & Goldberg, 2002) Apo A-I, which is located on the surface of HDL, serves as the main apolipoprotein and acts as a signal transduction protein for transporting free cholesterol from intracellular storage pools. HDL can also accept cholesterol released from lipolysis of triglyceride containing lipoproteins by a similar process. (Rosenson, 2003) After HDL takes up free cholesterol, it is then converted to cholesterol ester by LCAT, a plasma enzyme activated by Apo A-I. The conversion to cholesterol ester allows HDL to hold a larger capacity of cholesterol. The HDL then transfers the cholesterol ester to apo B lipoproteins, which are removed from the plasma by the liver. HDL can also be directly removed from the plasma by hepatocytes. (Tall, 1990) This process then completes reverse cholesterol transport which is thought to be the primary mechanism behind how HDL protects against atherosclerosis. Other protective mechanisms attributed to HDL include maintenance of endothelial function and protection against thrombosis by causing low blood viscosity through an action on red blood cell deformability. (Rosenson, Shott, and Tangney, 2001; Shah, Kaul, Nilsson, and Cercek, 2001)

Chapter Two Methods

A literature review was conducted primarily by electronic sources. Databases that were used for the literature search include: Medline, Pubmed, CINAHL, Health and Wellness Resource Center, and Google. Harrison's and UptoDate online were also utilized for reliable and accurate overviews on lipid metabolism. Keywords that were used for searching the databases include fatty acids, lipids, lipoproteins, LDL, LDL receptors, saturated fat, *trans*-unsaturated fat, polyunsaturated fatty acids, and monounsaturated fatty acids.

The scope of the research encompassed both animal and human studies from the year 1993 until the present. Other subjects of studies that were included besides effects of fatty acids on LDL regulation include dietary cholesterol as an intervening variable and effects of genetic variances on the response of LDL to dietary fatty acids. The search involved about fifty reliable studies of which thirty-nine were utilized in this literature review.

Chapter Three Literature Review

Studies with Saturated Fatty Acids

Dietary fatty acids have been found to play an important role in regulation of serum LDL levels and LDL metabolism. Several studies have shown that diets high in saturated fatty acids (SFA) increase LDL levels, which also increases an individual's risk for atherosclerosis. (Hajri, Kholza, Pronczuk, & Hayes, 1998; Fernandez, 1997; Mustad et. al., 1997; Bucci et. al., 1998; Hannah, Yasmane, Berlin, and Howard, 1995) These findings have been implemented into different measures of prevention and treatment of CHD ranging from elimination of all fats in the diet to substituting SFA with other fatty acids such as monounsaturated (MUFA) or polyunsaturated fats (PUFA). (Schaefer, 2000) Different saturated fatty acids include lauric (12C:0), myristic (14C:0), palmitic (16C:0), and stearic (18C:0). These fats do not have double bonds in their chemical composition and are a more solid form of fat found in animal based foods. (Schaefer, 2002) The mechanism of action behind their regulation of serum LDL levels involves reduced clearance of LDL from the blood by LDL receptors and overproduction of intracellular cholesterol. (Hajri et. al., 1998; Fernandez, 1997; Mustad et. al., 1997; Bucci et. al., 1998; Hannah et. al., 1995)

Overproduction of LDL.

The process of excessive LDL production is a primary consideration behind increased LDL levels from a SFA diet in many studies. One such study by Hajri et. al. utilized 48 gerbils that were randomized into two groups and challenged with either a (12:0 + 14:0) SFA or (18:2) PUFA for four to five weeks. They measured the serum lipoproteins, lipoprotein composition, particle size and isotope (¹²⁵) labeled LDL clearance. The data concluded that the fractional catabolic rate (FCR), which is a measure of serum LDL clearance, did not differ between the

SFA and PUFA groups. Particle composition and size also did not change between the two groups. (Hajri et. al., 1998)

Another study by Fernandez in 1997 utilized 48 guinea pigs and found similar results with an additional vitamin C deficiency as a variable. The animals were randomly assigned to one of six dietary groups for six weeks. The diets were of equal composition except for the independent variables of fat mix and vitamin C level. The activity of hepatic acyl CoA cholesterol acyltransferase (ACAT) increased, which is responsible for intracellular cholesterol production. This increased activity would result in an overproduction of LDL resulting in elevated serum LDL levels. However, their data also demonstrated that the increase in serum LDL was also caused by slower fractional catabolic rates (FCR) of LDL and higher LDL Apo B flux in addition to overproduction of LDL. These results show that both overproduction and ineffective LDL clearance have roles in the lipoprotein regulation by SFA. (Fernandez)

Reduced LDL clearance by receptors.

Other studies suggest that reduced LDL clearance from the plasma is the primary consideration behind elevated LDL levels from a diet high in SFA. One such study conducted by Mustad et. al. in 1997 utilized 25 healthy human subjects to isolate peripheral mononuclear cells and measure levels of LDL receptor protein. The study was a randomized, double blind, three way crossover design and involved diet periods of 8 weeks in length with 4-6 weeks between each period. The subjects were exposed to diets with different SFA concentrations; an all American Diet (AAD) consisting of 34% of calories as fat and 15% as SFA; a Step- One diet consisting of 29% of calories as fat and 9% as SFA; and a very low saturated fat diet consisting of 25% of calories as fat and 6% as SFA. The peripheral mononuclear cells were then isolated and ELISA was used to quantify LDL receptor protein on the cell membranes. The measured

amount of LDL receptor protein on cell membranes is an indirect measure of the abundance of LDL receptors on the cell. They found that the diets higher in SFA had the lowest amount of LDL receptors. These results suggest that diets higher in SFA cause high LDL levels due to a lower number of receptors for LDL clearance. (Mustad et. al.)

A similar study done by Bucci et. al. in 1998 studied binding, internalization, and degradation of isotope (125)labeled LDL in baby hamster kidney fibroblasts (BHK- 21 cells). BHK-21 cells were grown in 24 multiwell dishes to measure the binding of LDL to the LDL receptor, the internalization of LDL into the cell and the degradation of LDL once internalized into the cell. The cells were incubated with different free fatty acids. The SFA utilized include palmitic and stearic acids. The PUFA utilized include α -linolenic, linoleic, arachidonic, docosahexaenoic, and eicosapentaenoic acids. The *trans*- unsaturated fatty acid (TFA) utilized include elaidic acid. The MUFA utilized include oleic acid. They found that pre- incubation of BHK-21 cells with SFA (palmitic [16:0]) and stearic [18:0]) decreased binding, internalization and degradation of the (125) isotope labeled LDL, whereas, the PUFA, MUFA and TFA studied caused an increase in this activity. This concludes that free fatty acids do regulate LDL receptor activity in BHK- 21 cells, with SFA decreasing this cellular activity. (Bucci et. al.)

The next few studies oppose the conclusions made by previous studies of Mustad et. al. and Bucci et. al. that stated SFA decrease LDL receptor activity, which in turn reduces the amount of serum LDL that is cleared from the plasma. One such study by Hannah et. al. in 1995 utilized chinese hamster ovary (CHO) cell line. The CHO cells were incubated in dietary fatty acids such as 16:0, 18:0, which are SFA, 18:1, which is a MUFA, and 18:2, which is a PUFA. There was greater LDL binding affinity for cells grown in 16:0, 18:0, or 18:1 enriched media than for those grown in 18:2. However, the LDL receptor number was lower in the cells enriched

with SFA, but membrane fluidity was not affected. (Hannah et. al., 1995) This could suggest inhibited LDL receptor synthesis by the SFA due to the elevated amount of intracellular cholesterol. The difference in results of the two studies could be related to the different cell lines utilized and their methods of experimentation.

The results of many studies on the LDL receptor activity in response to SFA have been conflicting. A recent study by Pal et. al. in 2002 suggests that this fatty acid regulation of LDL metabolism occurs at the level of gene transcription and is supported by three different stages of expression. They utilized cultured human Hepatic G2 cells and measured functional cellular LDL binding activity, the amount of LDL receptor protein, and LDL receptor mRNA levels. It was found that the greater the unsaturation of the fatty acid, such as PUFA, the lower the LDL receptor binding activity, protein and mRNA levels. This supports the previous study that proposed that SFA do cause increased LDL receptor binding. In addition, the increased LDL receptor protein implies that SFA causes more LDL receptors on the cell surface. (Pal, Thomson, Bottema, and Roach, 2003)

Increase in LDL size.

Previous research has shown that a SFA diet can cause increased LDL size when the serum LDL levels increase. (Kratz, Gülbahçe, Cignarella, Assmann, & Wahrburg, 2002) This finding, if supported, would have made SFA less of a risk for CHD because the larger LDL particles are less atherogenic than the smaller, denser LDL. The smaller LDL particles are more susceptible to becoming oxidized which can directly result in atherosclerosis. (Campos, Dreon, and Krauss, 1995) Kratz et. al. examined the effects of dietary MUFA and PUFA on LDL particle size in healthy human participants. The participants were randomly divided into three groups for a parallel group design consisting of two consecutive diet periods. The diets were rich

in olive oil, a MUFA, Sunflower oil, a PUFA, or Rapeseed oil, a MUFA plus omega-3 PUFA. They found that dietary MUFA and PUFA similarly affect LDL size and a dietary change from saturated to unsaturated fat resulted in a slightly reduced LDL peak particle diameter. This would support the idea that SFA increases LDL size, however, the reduction in size after implementing unsaturated fats was so small that dietary fat was considered not a major factor affecting LDL size. (Kratz et. al. 2002)

A recent study by Rivellese et. al. in 2003 measured fasting lipoproteins and LDL size with various diets consisting of MUFA, SFA, and omega-3 PUFA. They utilized 162 healthy human participants and randomized them into a two groups. For 90 days one group was given a diet high in MUFA while the other was given a diet high in SFA. Additionally they randomized the participants further to receive either an omega- 3 PUFA supplementation of 3.6 grams per day or a placebo containing the same amount of olive oil. By measuring serum lipoproteins and LDL particle size, they found that both serum LDL and triglyceride levels decreased with the MUFA diet and increased with the SFA diet. The serum triglycerides decreased and the serum LDL increased significantly with the additional omega-3 PUFA supplementation. However, there was no change in LDL particle size with the two diets or n-3 supplements. Prior studies claiming change in LDL size with a high SFA diet may have been affected by an intervening variable if the carbohydrates were not kept equal in all diet periods. (Rivellese et. al.)

Another study conducted by Callow et. al. in 2002 examined the changes in LDL particle composition after consumption of various types and quantities of fatty acids. They proposed that the change in size or composition of LDL was associated with high triglyceride levels, especially during a postprandial period. This study used eight individuals in a balanced design that consumed three meals with one that was low in fat, another high in SFA, and another high in

PUFA. They found that the density and size of LDL particles did not change, but there was significant change in LDL composition. The lipid exchange during the postprandial period resulted in an increase in the triglyceride concentration of the LDL particles in exchange for stored cholesterol ester. This change in composition of LDL after meals represents a significant exchange of lipids with particles such as chylomicrons containing dietary fatty acids. (Callow, Summers, Bradshaw, and Frayn, 2002)

Studies with Trans Unsaturated Fatty Acids

Trans-unsaturated fatty acids (TFA) have become a recent subject of much research due to their adverse effects on serum lipoproteins. TFA are a synthetic product of chemical manipulation or hydrogenation of natural unsaturated fats that are in *cis* configuration. They were originally developed to replace saturated fats for a healthier and more convenient alternative in most factory processed foods because their consistency is also solid- like. However, many studies have shown that foods containing partially hydrogenated soybean oil or other *trans*- fatty acids have a more severe affect on serum lipoproteins than the saturated fats that they are supposed to be replacing. (Schaefer, 2002)

The mechanism behind the negative lipoprotein regulation of TFA is still unclear but many studies have supported the proposal that a diet high in *trans*- unsaturated adversely affects lipoproteins more than any other dietary fatty acids. (Dashti, Feng, Freeman, Ghandi, and Franklin, 2002; Sundram, French, and Clandinin, 2003; Sundram, Ismail, Hayes, Jeyamalar, and Pathmanathan, 1997) A recent study by Dashti et. al. in 2002 utilized human hepatoma HepG2 cells and examined the long term effects of linoleic (*cis* 18:2), a PUFA, linolelaidic (*trans* 18:2), a TFA, elaidic, (*trans* 18:1) a TFA, and palmitic (16:0), a SFA, on hepatic lipoprotein production. Hepatic G2 cells were incubated in the 0.1 mmol/L of each fatty acid for five to six

days. They found that the *trans*- fatty acid incubation resulted in the highest mass ratio of ApoB/ApoA and the highest secretion and cellular accumulation of free cholesterol and cholesterol esters. The SFA increased the LDL concentration 17%, whereas the TFA increased the concentration 154%. These results show that TFA cause higher intracellular synthesis and and serum LDL levels resulting in a higher risk for atherosclerosis and CHD (Dashti et. al., 2002)

There was only one study done by Lichtenstein et. al. that demonstrated a decrease in LDL levels with a *trans*- fat diet. The diet consisted of margarine or shortening when compared to a diet high in saturated fat or butter. Eighteen human participants consumed six different diets consisting of soybean oil, semiliquid margarine, soft margarine, shortening, stick margarine, or butter for 35 days each. The mean LDL was 177 and HDL was 45 with the butter enriched diet. The serum LDL was reduced similarly by all the butter substitutes with soybean oil reducing LDL the most. The serum HDL was also reduced similarly by all the butter substitutes with stick margarine reducing HDL the most. The decrease in serum LDL by the TFA diet was also accompanied with a significant decrease in serum HDL levels, which negates any cardiovascular benefit the improvement in LDL levels could have. (Lichtenstein, Ausman, Jalbert, and Schaefer, 1999) Unlike SFA, TFA have been shown to decrease serum HDL levels in other research studies as well, which is a cardiovascular risk factor independent of increased LDL levels. (Sundram, French et. al., 2003; Sundram, Ismail et. al., 1997)

Another study by Bucci et. al. that was mentioned previously compared oleic, a MUFA and elaidic, its *trans* counterpart. They found that both oleic and elaidic, its *trans* increased binding, internalization, and degradation of isotope labeled LDL in BHK- 21 cells. Although the MUFA increased the cellular activity more than the TFA, these results demonstrated that dietary *trans* fats can regulate LDL receptor activity. (Bucci et. al., 1998)

Studies with Mono- and Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA) have been labeled as more cardio-protective based on the numerous studies suggesting that they lower serum LDL levels and sometimes raise HDL levels. (Schaefer, 2002) PUFA have more than one double bond in their chemical composition, whereas MUFA have only one double bond. Both fatty acids are more liquid in their natural form. The most common type of MUFA is oleic (18:1) and is found in foods such as olive oil and canola oil. Some common PUFA include linoleic acid (18:2), arachidonic acid (20:4), eicosapentanoic acid (20:5) and docosahexaenoic (22:6). These fatty acids can be found in foods such as tree nuts, fish, and vegetable oils. PUFA can be further classified as omega-9, omega-6, and omega-3 based on where their double bonds are located on the carbon chain. (Schaefer, 2002)

Although PUFA have been shown to decrease LDL levels, some studies have shown that they have negative effects on oxidation status. One such study by Bayindir et. al. compared the effects of dietary SFA, MUFA, and PUFA on serum lipids, oxidant stress, prostanoid synthesis, and aortic histology in rabbits. The animals were randomly grouped to receive either corn oil, a PUFA or olive oil, a MUFA. They found that corn oil improved the lipid profile, but increased oxidant stress and induced endothelial damage. The olive oil had no effect on oxidation of lipids or endothelial function, but similarly improved the lipid profile. This demonstrates that MUFA are more effective than PUFA for protection of endothelial integrity. (Bayindir et. al., 2002) An additional study done by Večeřa et. al. utilized rats that were randomized into two groups to receive a three week diet of either currant oil, consisting of both n-3 and n-6 PUFA or lard fat, a product of both SFA and MUFA. They found that the serum lipoproteins had not significantly improved in either group. However, there was an accumulation of liver triglycerides in the lard

fat group and none in the currant oil group. They also found that currant oil had adverse effects on antioxidant status when compared to lard fat. This implies that PUFA pose a negative effect on antioxidant status when compared to MUFA or SFA. (Večeřa et. al., 2003)

Other studies have examined the effect that PUFA have on LDL metabolism with and without addition of antioxidant vitamins and have suggested that PUFA effectively downregulate LDL receptor activity alone and is based on regulation of mRNA and gene transcription. (Pal, Bottema, and Roach, 1997; Pal, Thomson, Bottema, and Roach, 2002) The first study conducted in 1997 by Pal et. al. included the effects of antioxidant vitamins A, β -carotene, C and E on the receptor regulation by PUFA. Hepatic G2 cell cultures were incubated with linoleic acid, a PUFA, and eicosapentaenoic acid (EPA), an omega-3 PUFA for 48 hours. The independent variable was the addition of vitamin A, β -carotene, vitamin C, or vitamin E to the incubation. Methods utilized for measuring LDL receptor activity include colloidal gold LDL conjugates, western blotting, southern blotting, and PCR amplification. They found that LDL receptor activity decreased after incubation in PUFA with or without the additional vitamins, which implies that the fatty acids cause this downregulation and not their oxidation products. Incubation with the vitamins alone also decreased receptor activity, mass, and mRNA levels. With support from their previous studies, they concluded that effects from antioxidants and fatty acids on LDL receptors are independent from each other. (Pal et. al., 1997)

Another study by Pal et. al. in 2002 examined the effect of different fatty acids on the LDL receptor of cultured human Hepatic G2 cells without the addition of vitamins. Effects were measured at three stages of expression including functional cellular LDL binding activity, the amount of LDL receptor protein and the LDL receptor mRNA level. The HepG2 cells were incubated for 24 hours with oleic acid, a MUFA, palmitic acid, a SFA, linoleic acid, a PUFA or

eicosapentaenoic acid (EPA), an n-3 (omega 3) PUFA for 24 hours. The measuring of LDL receptor activity was similar to the methods utilized by the previous study in 1997 by Pal et. al.. They found that the higher the saturation of the fats, with EPA (20:5) being the least saturated and palmitic acid (16:0) being the most, the higher the binding activity of LDL receptor, the level on mRNA, and the level of receptor protein. This implies that the PUFA effectively downregulate the activity of LDL receptors on HepG2 cells when compared to SFA. Therefore, the effects of these fatty acids were found to regulate LDL metabolism at the level of gene transcription. (Pal et. al., 2002)

One specific type of PUFA, omega-3 or n-3, has been found in many studies recently to be beneficial to cardiovascular health. Some common n-3 PUFA include α -linolenic (18:3), eicosapentaenoic (20:5), and docosahexaenoic (22:6), which are found in foods such as flaxseed oil, fatty fish and walnuts. (Schaefer, 2000) Many studies have concluded that these PUFA help to decrease triglyceride levels and increase HDL levels. However, LDL levels tend to elevate slightly with n-3 fatty acid supplementation as in the study by Rivellese et. al that was discussed previously. (Rivellese et. al., 2003; Schaefer, 2000)

A study conducted by Spady et. al. in 1995 with the hamster and rat examined the regulatory effects of dietary n-3 PUFA on hepatic LDL uptake. The n-3 supplementation was given as 3%, 12%, or 24% of daily calories and compared with n-6 supplementation as 12% daily calories for one month. This study measured the effect on lipoprotein levels, LDL uptake rates for receptor dependent and receptor independent uptake, and chylomicron clearance rates to determine if n-3 PUFA alters the activity of the chylomicron remnant receptor. They found that the regulation of dietary n-3 PUFA varies considerably from species to species. In the rat, triglycerides and total cholesterol decreased with the lower fat n-3 diet. The high fat diet also

caused total cholesterol to fall, but HDL levels had the largest reduction. In the hamster, cholesterol was lowered minimally and the triglycerides were not affected in the lower fat n-3 diet. In the high fat diet, LDL levels increased while HDL levels decreased. The n-6 diet did not affect cholesterol in the hamster or rat. The receptor- dependent LDL uptake rate increased during both high and low fat n-3 diets in the rat. However, in the hamster, the receptor- dependent uptake was not affected by the low fat n-3 diet and was even suppressed by the high fat diet. The receptor- independent LDL uptake was not affected by either experimental diets or animals and there was no change in the chylomicron clearance rates. This study also showed that the suppression of the LDL receptors in the hamster was accompanied by similar changes in LDL receptor protein and mRNA. This supports other studies in that dietary fats regulate hepatic LDL receptor activity possibly at the level of gene transcription. However, the same relationship with the rat was not seen when LDL uptake rate increased two fold in response to dietary n-3. (Spady, Horton, and Cuthbert)

A study by Bucci et. al. that was mentioned previously examined the effects of fatty acids on BHK- 21 cells. The BHK- 21 cells were incubated in various fatty acids including docosahexaenoic acid, eicosapentaenoic acid and α -linolenic acid. They found that n-3 PUFA increased binding and activity of the LDL receptor with docosahexaenoic and eicosapentaenoic being more effective than α -linoleic acid. These conclusions conflict with previously mentioned studies by Pal et. al., which claim that PUFA downregulate or decrease LDL receptor activity. (Bucci et. al., 1998; Pal et. al., 2002; Pal et. al., 1997)

A different study by Schmid & Woollett examined the effects of PUFA on sterol synthesis rates in adult and fetal tissues of the hamster. They found that adult cholesterol balance was neutral while the fetal cholesterol balance was usually negative due to the state of

rapid cell growth and excessive need for cholesterol. Results demonstrated that adult hepatic sterol synthesis rates decrease by 60% when the liver is enriched with PUFA, whereas, the fetal synthesis rates are not affected. If the fetal tissue had the same response as the adult, there would be a definite deficiency in cholesterol for cell growth resulting in defects at birth. (Schmid & Woollett, 2003)

Studies considering dietary cholesterol

Dietary cholesterol acts as an important confounding variable in many studies examining the effects of dietary fatty acids on lipoprotein metabolism. A study done by Stucchi, Terpestra, and Nicolosi in 1995 examined the effect of dietary cholesterol in addition to various fatty acids on LDL metabolism in cynomolgus monkeys. Twenty monkeys were randomized into two groups for a parallel group design. The first group was fed 30% and the second 36% of total calories as fat. Both received three different levels of dietary cholesterol as egg yolk which consisted of a low level with .01 mg/kJ for 30 weeks, a medium level with .03 mg/kJ for 32 weeks, and a high level with .05 mg/kJ for 24 weeks. MUFA and PUFA were held constant. SFA was given as palmitic or lauric with myristic in the high fat diets. They found that dietary cholesterol increased in a dose dependent manner resulted in an increase in serum LDL, apolipoprotein B, and total cholesterol in both experimental groups. These increases were due to elevated LDL apo B production rates in addition to the reduced amount of fractional clearance rate of LDL apo B from the blood stream. Apo A-I and HDL concentrations were not affected significantly by the dietary cholesterol. The cynomolgus monkeys are more responsive to dietary cholesterol when compared to humans and represent a good model for future studies on lipoprotein metabolism sensitivity to dietary cholesterol. (Stucchi, Terpestra, & Nicolosi) Most studies on the effects of dietary fatty acids on LDL metabolism keep dietary cholesterol constant

in all experimental groups or eliminate it from the diet to isolate the effects of the fatty acids alone.

Studies with Genetic Variances

Several gene polymorphisms have also been attributed to different individual responses to dietary fatty acids. Some genetic variances that cause various individual responses to fatty acids include Lp (a) polymorphisms, apo A-I gene promoter mutations, ApoCIII polymorphism, and different Apo E genotypes. (Mata et. al., 1998; Tsai, Park, & Snook, 1998; Wallace et. al., 2000; Weggemans, Zock, Ordovas, Pedro- Botet, & Katan, 2001 Brown, Ordovas, and Campos, 2003)

Mata et al. conducted a study on the human apolipoprotein A-I gene promoter and examined its effect on serum LDL levels when exposed to different dietary fats. An initial 28 day period involved 26 men and 24 women consuming a high saturated fat diet. A second and third period involved a high MUFA diet and a high PUFA diet respectively for 35 days each. This study found that the G/A mutations were associated with the variability of LDL concentration response to diet modification. Individuals with the A allele had a more significant decrease in LDL after SFA were replaced with PUFA than homozygotes with the G allele. The apolipoprotein E genotype was also studied and was not found to be associated with LDL responsiveness to diet. Overall, the G/A polymorphisms had a small but significant effect on serum LDL levels in response to dietary fatty acids. The A allele responsible could have a direct effect on Apo A-I expression or it could be in close approximation of a functional mutation of the Apo CIII or Apo AIV genes. (Mata et. al., 1998)

Another study by Tsai et. al. in 1998 examined the effects of lipoprotein (a) polymorphisms on the response of serum LDL levels, LDL receptor uptake, and degradation of

LDL during a PUFA and SFA diet. Eighteen females were involved in a two way crossover study after being on one week of a baseline PUFA diet. The high saturated fat diets consisted of four weeks of either medium chain triglycerides (8:0 + 10:0) or lauric acid (12:0). They found that the Lp(a) polymorphism did not effect serum LDL, LDL receptor uptake, or degradation of LDL on the baseline PUFA diet. This suggests the Lp (a) polymorphism does not affect LDL metabolism. (Tsai et. al.)

In 2000, Wallace et. al. examined different gene polymorphisms such as lipoprotein lipase, cholesterol ester transfer protein, apolipoprotein B, and apolipoprotein AIV and their effects on the response of serum LDL concentration to diets high in SFA or PUFA. The study involved 46 free living individuals in a crossover trial with two four week periods consisting of a high SFA diet with 21% total calories and a high PUFA diet with 10% of total calories. The study showed that Apo AIV was the only gene polymorphism that displayed a significant response to dietary change. The Apo AIV polymorphism caused a dramatic decrease in serum LDL concentration when SFA was substituted with PUFA. This gene polymorphism represents about 10% of the population and individuals with this variance would highly benefit from a diet high in PUFA and low in SFA. (Wallace et. al.)

The study mentioned previously by Mata et. al. concluded that the apolipoprotein E polymorphism did not affect the responsiveness of serum LDL levels to dietary fat. Another more extensive study conducted by Weggemans et. al. isolated participants with apolipoprotein E and examined the response of serum LDL levels to dietary fat and cholesterol from data that was pooled from 26 previous controlled trials. DNA was collected from 549 previous human participants that were able to be located. They found that individuals with the Apo E 3/4 and Apo E 4/4 genotype had a greater response or increase in serum LDL with the SFA diet that

those with the Apo E 3/3 genotype. However, the Apo E genotype effects on serum LDL were very small and the knowledge of an individual's genotype alone would not be sufficient for treatment and therapeutic management of high cholesterol. (Weggemans et. al., 2001)

The Apo CII gene promoter polymorphisms were also studied for their effects on serum lipoproteins response to high SFA diets. Brown et. al. in 2003 utilized 336 randomly selected individuals from Costa Rica who were genotyped into three different Apo CIII polymorphisms. Dietary assessment was measured with a food frequency questionnaire (FFQ) that was designed specifically for this population. Participants recalled what they ate in the last 24 hours, what type of foods and cooking oils they use in the home, and what they eat outside the home. Apo CIII genotypes were determined by using allele specific oligonucleotide hybridization PCR and PCR-amplification. They found that only one polymorphism, the Apo CIII promoter 455T- 625T, was found to have a significant response to dietary SFA. There was a 13% increase in total cholesterol and a 20% increase in serum LDL with the SFA diet. (Brown et. al., 2003)

Therefore, individuals with the Apo CIII promoter 455T- 625-T polymorphism would benefit the most from a diet consistently low in saturated fat.

Chapter Four Discussion & Conclusions

Dietary fatty acids have been shown to effectively regulate serum lipoprotein levels in different ways. The mechanism responsible for this cellular regulation is still under investigation. The serum LDL concentration represents a balance between removal of LDL from the blood by LDL receptors and LDL production. Increase in LDL concentrations is thought to be due to the decrease in hepatic LDL receptor activity in addition to the overproduction of LDL. Some studies argue that the LDL concentration increase is primarily due to dietary saturated and *trans*-unsaturated fatty acids regulating the activity of the LDL receptors and therefore, decreasing LDL clearance from the blood. (Bucci et. al., 1998; Mustad et. al., 1997) Other studies claim that the rate of production of LDL is increased by these fatty acids and, therefore, is primarily responsible for the increase in LDL concentrations. (Hajri et. al., 1998; Fernandez, 1997)

Dietary SFA have been shown to increase the intracellular cholesterol production by increasing the activity of acyl CoA cholesterol acyltransferase, which then increases serum LDL. (Dashti et. al., 2002; Hajri et. al., 1998) Alternatively, the studies on the LDL receptor have been quite conflicting in that many have found SFA to decrease LDL receptor activity and number while others demonstrate the opposite. Recent studies such as those done by Pal et. al. in 1997 and 2002 have shown that the more unsaturated fatty acids downregulate receptor activity, whereas SFA tend to increase LDL receptor binding and synthesis. (Pal et. al., 2002; Pal et. al. 1997) Therefore, saturated fat increases serum LDL levels primarily by increasing intracellular cholesterol synthesis so that the balance of production and clearance is no longer stabilized. so that the balance of production and clearance is no longer stabilized. Additionally, there has been no relationship found between the dietary effects of SFA and LDL particle size. This implies that

the larger LDL particles, which are less atherogenic than the smaller, are not a result of a diet high in SFA. (Rivellese et. al., 2003; Kratz et. al., 2002)

Polyunsaturated fatty acids, such as linoleic or arachidonic acid, and monounsaturated fatty acids, such as oleic acid, are believed to have an opposite effect on the LDL receptors when compared with saturated and *trans*-unsaturated fat. Recent studies have shown that PUFA in the diet effectively downregulate the LDL receptor expression and activity. (Pal et. al., 2002)

Considering past research, this information may sound conflicting because downregulation of the LDL receptor would cause a higher serum LDL level due to decreased FCR. Additionally, this is the mechanism of action that many studies have proposed as the reason SFA in the diet increases LDL levels. However, many studies have shown that replacing the dietary saturated and *trans* unsaturated fats with omega-3 or 6 polyunsaturated fats will reduce LDL levels and therefore decrease the risk of cardiac morbidity and mortality. The exact mechanism behind this regulation is still unclear. Although PUFA have shown to improve serum LDL, there have also been negative impacts demonstrated on oxidation status of these lipids, including increased susceptibility of becoming oxidized, increase in formation of free radicals, and depletion of endogenous antioxidants. This negative effect on oxidation status can eventually lead to atherosclerosis of the vessels and in turn increase cardiac morbidity and mortality. MUFA have been found to be more neutral regarding LDL metabolism and oxidation. They do not affect oxidation status but do cause mild improvements on the lipoprotein profile. (Večeřa et. al., 2003; Bayindir et. al., 2002) Unfortunately, the proven benefits from MUFA come mostly from epidemiological data and risk factor analysis. MUFA have not been isolated in studies enough to recommend that they substitute for PUFA in the diet. Both PUFA and MUFA have been found to decrease serum LDL levels and should substitute SFA in the diet. Their effect on serum HDL is

less clear and represents an area for future research also. The mechanism of action of HDL and Apo A-I metabolism are still being examined. More knowledge on HDL may give insight about the exact impact that these dietary fatty acids have on regulation of lipoprotein levels.

Trans-unsaturated fatty acids represent a more recent discovery on cardiovascular risk factors. TFA have been shown to decrease serum HDL levels in addition to raising serum LDL levels. These fatty acids have also been proposed to regulate LDL metabolism in a similar mechanism to their *cis*-unsaturated counterparts. There has been no other dietary fatty acid found to have such a profound impact on serum lipoproteins. TFA lowers serum HDL more significantly than any other fatty acid studied, which represents a significant risk factor for CHD. (Sundram et. al., 1997; Dashti et. al., 2002, Sundram et. al., 2003) Due to these findings, European food processing companies have been forced to eliminate *trans*-fatty acids in their consumer products. American food manufacturers have not had such restrictions placed, so the majority of packaged and process food products in the United States still contain *trans*-fatty acids. The FDA will soon be enforcing nutrition labeling for *trans*-fat quantity in products as the general public is now becoming more aware of the implications of these fatty acids. (Schaefer, 2000) There is still much to gain from further research on TFA. Very little is known about the regulation of LDL metabolism by dietary TFA. However, most studies have supported the negative effects of TFA on both serum LDL and HDL levels. Research studies on TFA have already proven their detrimental effect on cardiovascular health and must be made known to the general public and enforced nationally to treat and prevent cardiac morbidity and mortality.

Several genetic variances have been studied with only a few found to be associated with significant serum lipoprotein responses to dietary fatty acids. Some of the important gene polymorphisms that have been identified include Apo AIV and the G/A polymorphism of the

Apo A-I gene promoter. Both of these variances cause a significant decrease in LDL levels when SFA are substituted with PUFA in the diet. Such gene polymorphisms are an underlying risk factor for hyperlipidemia and eventually cardiac morbidity or mortality. (Mata et. al., 1998; Wallace et. al., 2000) Once genotype testing becomes more widely utilized, it will be important to screen for these genetic variances because they may highly benefit from supplementing more PUFA into their diet to treat lipid disorders.

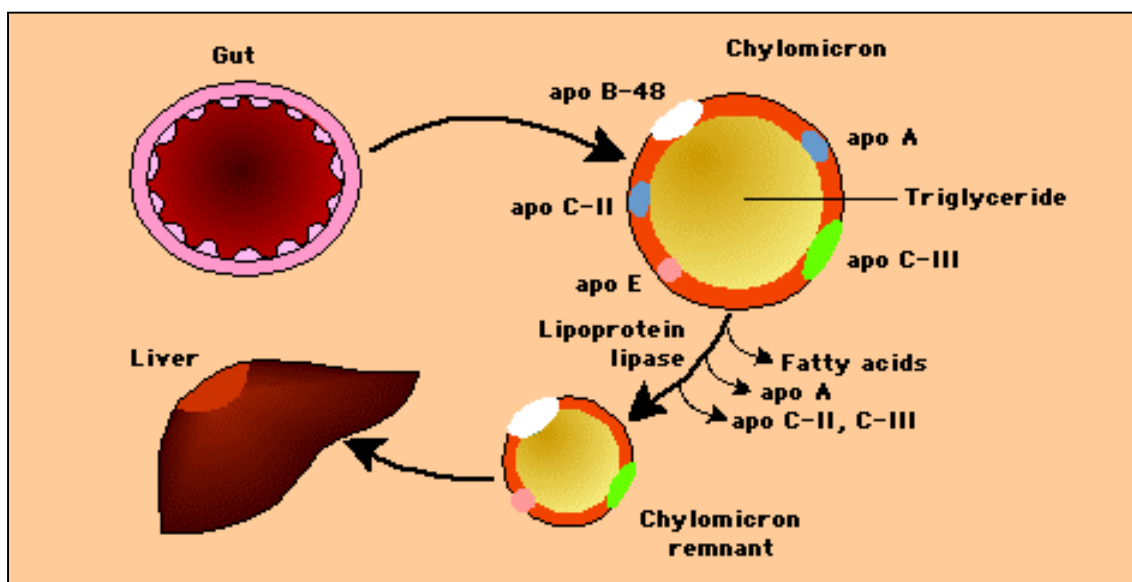
New and more advanced methods are now being utilized to study LDL metabolism and LDL receptor activity. The detection of LDL receptor binding is being measured with an enhanced colloidal gold labeling procedure. Chylomicron remnants are labeled with colloidal gold, which has made it easier to identify receptor expression than with the previous gold conjugated LDL. This research is important because LDL receptor deficiency may be the underlying cause of many hyperlipidemic conditions and in the past it has been difficult to measure LDL receptor activity. (Pal, Elsegood, Pector, & Mamo, 2000)

More research is needed on the effects of dietary MUFA and TFA. There is already sufficient epidemiological studies demonstrating the effects and cardiovascular risks or benefits of consuming these fatty acids, but little is known about their mechanism of action of LDL metabolism. Another important subject area for future research would be the metabolism of serum HDL. There is a lot of information already established on LDL metabolism, but HDL is part of the same process of balancing serum lipoprotein levels. HDL also represents an important part of treatment and prevention of cardiovascular disease, yet so little is known about its mechanism of action.

Overall, many factors can affect the metabolism of serum lipoproteins and alter the balance between lipoprotein clearance and production. Once this balance becomes unstable

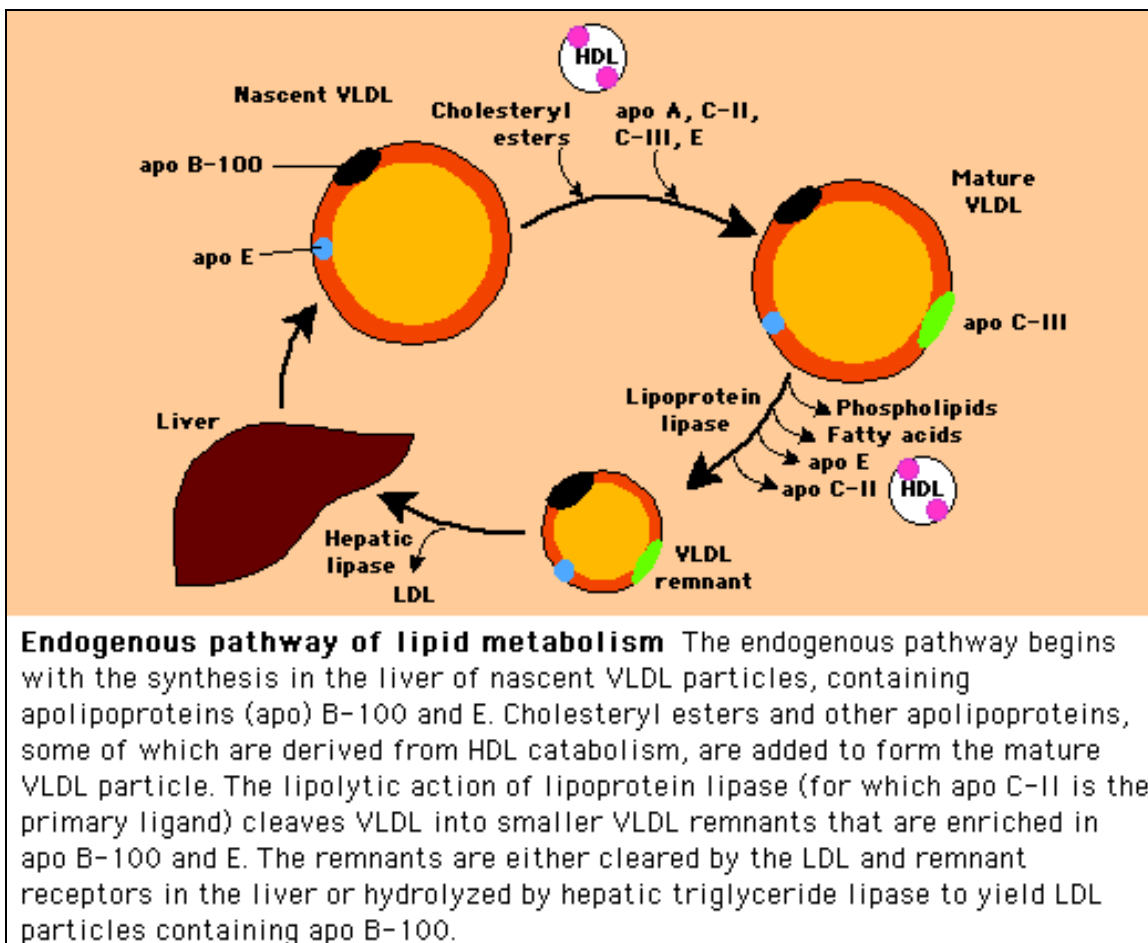
levels of lipoproteins can become altered resulting in cardiovascular disease. Once this area of research in lipid metabolism is defined, many changes and recommendations can be made in the healthcare system. Patients can be accurately educated and advised regarding their nutritional choices. Dietary fatty acids are essential nutrients that, in the right quantity and quality, can improve cardiovascular health.

Figure 1



Exogenous pathway of lipid metabolism In the intestinal cell, absorbed free fatty acids combine with glycerol to form triglycerides, and, to a lesser degree, absorbed cholesterol is esterified to form cholesteryl esters. These lipids are assembled as chylomicrons; the main apolipoprotein (apo) is B-48, but apo C-II and E are acquired as the chylomicrons enter the circulation. Apo C-II is a cofactor for lipoprotein lipase which makes the chylomicrons progressively smaller in part by hydrolyzing the core triglycerides and releasing free fatty acids. The chylomicron remnants that are cleared from the circulation by hepatic chylomicron remnant receptors for which apo E is a high-affinity ligand.

Figure 2



Robert S. Rosenson Lipoprotein classification, metabolism, and role in atherosclerosis
Up to date 2004 figure (one and two)

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Effects of Dietary Fatty Acids on Serum LDL Levels and LDL Metabolism

Brandi M. Kraus

Abstract

Objective. Dietary fatty acids have been found to regulate serum lipoprotein metabolism. Epidemiological studies have shown that diets high in saturated (SFA) and *trans*-unsaturated fatty acids (TFA) increase serum low density lipoprotein (LDL) levels, whereas, diets high in poly- (PUFA) and monounsaturated fatty acids (MUFA) lower serum LDL levels. A review of the literature was completed to explain the cellular processes responsible for serum LDL regulation, which have been examined in several human and animal models. Method: Databases include CINAHL, Health and Wellness Resource Center, MEDLINE, and Pubmed. Results: SFA increases intracellular cholesterol production, whereas, its effects on LDL receptor activity have been conflicting. SFA have been found to both inhibit and increase LDL receptor activity and synthesis. PUFA downregulate LDL receptors and gene transcription, but cause more susceptibility to oxidation. MUFA also have beneficial effects on LDL but do not show susceptibility to oxidation. Conclusion: MUFA may be the best alternative to replace SFA and TFA.