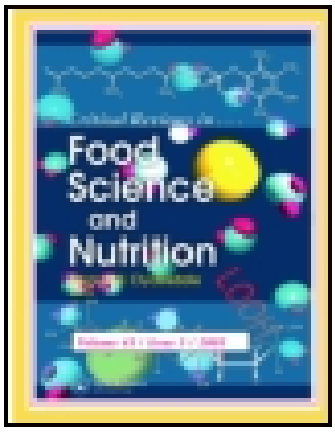

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The Role of Dietary Cholesterol in Lipoprotein Metabolism and Related Metabolic Abnormalities: A Mini-review

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ABSTRACT

Cholesterol plays a vital role in cell biology. Dietary cholesterol or ñexogenousò cholesterol accounts for approximately one-third of pooled body cholesterol, and the remaining 70% is synthesized in the body (endogenous cholesterol). Increased dietary cholesterol intakes may result in increased serum cholesterol in some individuals, while other subjects may not respond to dietary cholesterol. However, diet-increased serum cholesterol levels do not increase the low density lipoprotein / high density lipoprotein (LDL/HDL) cholesterol ratio, nor do they decrease the size of LDL particles or HDL cholesterol levels. Elevated levels of LDL cholesterol, reduced HDL cholesterol levels and small, dense LDL particles are independent risk factors for coronary artery disease. Dietary cholesterol is the primary approach for treatment of conditions such as

Smith-Lemli-Opitz syndrome. Recent studies have highlighted mechanisms for absorption of dietary cholesterol. These studies have help understand how dietary and/or pharmaceutical agents inhibit cholesterol absorption and thereby reduce LDL cholesterol concentrations. In this article, various aspects of cholesterol metabolism, including dietary sources, absorption, and abnormalities in cholesterol metabolism have been summarized and discussed.

Keywords: Dietary Cholesterol; cholesterol metabolism; LDL / HDL cholesterol; coronary artery disease.

INTRODUCTION

Cholesterol is a member of biological lipids made primarily by animals and humans. It contains 27 carbon atoms, forming a 4-ring-nucleous and a side chain. The presence of four fused rings makes cholesterol a steroid compound. Cholesterol contains 2 double bonds, and therefore, it is an unsaturated lipid. Cholesterol is a hydrophobic compound and cannot be transported by itself in the blood circulation in animals and humans. Thus, it is combined with other compounds to form various lipoprotein particles. Among many types of lipoprotein particles, LDL, HDL and very low density lipoprotein (VLDL) contain the highest amounts of circulating cholesterol in the body. Chylomicrons are another type of lipoprotein formed by intestinal cells and primarily carry dietary lipids, including cholesterol.

Approximately 30% of whole body cholesterol comes from dietary sources; vegan individuals may not have cholesterol in their diets. Therefore, a tight regulation in the proportion of dietary cholesterol to total body cholesterol pool must be in place to regulate a steady state of circulating blood cholesterol levels. This may indicate that increases in ñexogenousò cholesterol levels are accompanied by decreased ñendogenousò cholesterol synthesis. However, in infancy the majority of the body cholesterol pool comes from dietary sources, as the body organs may not be well developed to synthesize enough ñendogenousò cholesterol. Similarly, old individuals may have decreased rates of cholesterol synthesis due to age-related reduced organ function or diseases. These conditions highlight the importance of adequate amounts of dietary cholesterol for the purpose of wellbeing and normal body function. On the other hand, the general population, as well as health care professionals, may be concerned about the health deteriorating effects of dietary cholesterol, particularly if high amounts are consumed regularly. The

American Heart Association recommends no more than 300 mg dietary cholesterol per day for the general population and less than 200 mg per day for cardiovascular subjects (Lichtenstein et al., 2006).

Cholesterol is found in the body in two forms of ñfreeò and ñesterifiedò with a general ratio of approximately 3:7. **Figure 1** illustrates the chemical structures of these 2 forms of cholesterol. Cholesterol is an important element in cell membranes which regulates their permeability and stability. Cholesterol is used to generate several other vital molecules including corticosteroids, sex hormones and vitamin D. Cholesterol is also used to produce bile acids which facilitate lipid digestion and absorption. Either too little or too much body cholesterol is a risk factor for disease development. For example, it is reported that low levels of LDL cholesterol may increase the risk for abnormalities such as cancer, premature birth, anxiety and depression (Fang et al., 2013). On the other hand, elevated levels of LDL cholesterol may increase the risk for coronary artery disease and stroke (LaRosa et al., 2013). The purpose of this review article was to summarize information on the role of dietary cholesterol in health and disease as well as factors regulating cholesterol homeostasis and metabolism.

DIETARY CHOLESTEROL AND CARDIOVASCULAR RISK

Many genetic and environmental risk factors have been identified for the development of cardiovascular disease. Among modifiable risk factors, circulating cholesterol concentrations have been recognized as a major risk factor for atherosclerotic cardiovascular disease. Several early large clinical studies suggested a positive association between total and LDL-cholesterol levels and coronary artery disease, while HDL-cholesterol levels were negatively associated with

the incidence of the disease (Castelli et al., 1977; Gordon et al., 1977). With advances in our understanding of the pathophysiology of the disease and lipoprotein metabolism, additional lipoporptoein biomarkers including non-HDL-cholesterol levels, the ratio of LDL/HDL cholesterol, total/HDL cholesterol and/or the levels or ratio of apolipoproteins B and AI, have been suggested for risk assessment and disease prognosis. However, the appropriateness of these biomarkers for risk assessment and treatment targets seems to be influenced by other factors including presence of other chronic abnormalities such as diabetes and the treatment strategies. For example, Kastelein and colleagues suggested that non-HDL cholesterol and apolipoprotein B can be used as target biomarkers of lipid-lowering therapy in cardiovascular patients (Kastelein et al., 2008).

Circulating lipoprotein cholesterol concentrations can be modified not only by drug therapy, but also by diets and lifestyle; one of these factors is dietary cholesterol. The degree to which serum cholesterol is increased by dietary cholesterol depends upon whether the individual's cholesterol synthesis is stimulated or down-regulated by increased intake of dietary cholesterol; the extent to which each of these phenomena occurs varies from person to person (Jones, 2009). The impact of dietary cholesterol on increasing cardiovascular risk has not been fully established. While some studies reported a positive association in this regard, others do not support such relationship (Heron et al., 2003; Mutungi et al., 2008).

The primary carrier of dietary (exogenous) cholesterol is chylomicron particles, while the primary carrier of endogenous cholesterol is LDL particles. There are fundamental differences between chylomicron and LDL particles in regard to their production and metabolism. Among

them, the presence of apolipoportien B_{100} in modified LDL particles makes this lipopoprtien to be up taken by macrophages through scavenger receptors initiating foam cell formation. Such mechanism is the basis of conclusions from major clinical, interventional and epidemiological studies that elevated LDL-cholesterol levels are an independent risk factor for coronary artery disease. Such strong evidence does not exist for atherogenic properties of chylomicron particles. Thus, it seems reasonable to suggest that the impact of dietary (endogenous) cholesterol in pathophysiology of atherosclerosis may be different from that of ñendogenousò cholesterol.

Foods with an animal origin contain cholesterol to varying degrees. **Table 1** summarizes major sources of dietary cholesterol (Health Canada, 2010a). Cholesterol in food can be found in ñfreeò and ñesterifiedò forms. While ñfreeò cholesterol is ready to be absorbed, the ñesterifiedò cholesterol needs to be broken down to corresponding fatty acids and cholesterol moieties. Some types of these fatty acids are strong stimulators of cholesterol synthesis. For example, palmitic and stearic acids may stimulate cholesterol synthesis more than other dietary fatty acids may (Gibbons, 2003). Therefore, not only the cholesterol contents of food may raise circulating cholesterol levels, but fatty acid-induced cholesterol biosynthesis can also contribute to diet-increased serum cholesterol concentrations. It is interesting to note that the impact of dietary cholesterol alone on raising total blood cholesterol concentrations varies among individuals. The ñhyper-respondersò absorb dietary cholesterol more efficiently than the ñhypo-respondersò do (McNamara et al., 1987). It has been shown that the levels of both LDL and HDL cholesterol rise in the ñhyper-responderò subjects following consumption of dietary cholesterol (Heron et al., 2003); this increase in lipoprotein particle cholesterol concentrations does not change the ratio of LDL/HDL cholesterol levels (Heron et al., 2002). Similarly, the levels of serum cholesterol will

not significantly change in the ñhypo-responderò subject (Fernandez, 2010). Thus, altogether, consumption of dietary cholesterol may not significantly increase cardiovascular risk as the LDL/HDL ratio remains unchanged regardless of the extent of response to dietary cholesterol.

Another study reported that consumption of approximately 200 mg of dietary cholesterol per day may raise the levels of HDL cholesterol (Mayurasakorn et al., 2008). Such an increase in HDL cholesterol levels in the presence of unchanged LDL cholesterol levels will reduce the LDL/HDL cholesterol ratio, and thereby, may reduce cardiovascular risk. Furthermore, it has been reported that overweight subjects respond to dietary cholesterol only by increasing the HDL cholesterol levels (Mutungi et al., 2008). Twelve weeks of consumption of up to 550 mg of additional dietary cholesterol did not increase LDL cholesterol levels, but significantly increased HDL cholesterol levels in subjects with confirmed metabolic syndrome (Blesso et al., 2012). It is interesting that patients with metabolic syndrome are among those with defined cardiovascular risk and are recommended to consume no more than 200 mg of dietary cholesterol per day.

Not only are the levels of LDL cholesterol among the well-established cardiovascular risk factors, but their size also plays a crucial role in this regard. Individuals with pattern ñBò lipoprotein have small dense LDL particles (Krauss, 2001), while in pattern ñAò the size of LDL particles is large (Mensink and Katan, 1992). It is generally well established that small dense LDL particles are more atherogenic than large LDL particles (Gardner et al., 1996). Evidence suggests that increased dietary cholesterol intakes may increase the size of LDL particles, and reduce the numbers of small dense LDL particles (Zanni et al., 1987).

Similarly, increased numbers of large HDL particles have been reported after dietary cholesterol intake (Romano et al., 1998). Large HDL particles are known to be negatively associated with cardiovascular risk (Mora et al., 2009). Such an increase in HDL particle size following consumption of eggs does not seem to be dependent on the response of subjects, as both ñhyper-respondersò and ñhypo-respondersò similarly increased their numbers of large HDL particles after consumption of 3 eggs for 4 weeks (Greene et al., 2006). Moreover, increases in HDL particle size after cholesterol consumption have been observed in a variety of patients including those with high body mass index (BMI) and hypercholesterolemia as well as in normocholesterolemic individuals (Clifton et al., 1990).

Increased size and cholesterol concentrations of HDL particles may indicate changes in cholesterol-reverse transport (CRT) mechanisms. CRT may be considered as an anti-atherogenic pathway by which peripheral cholesterol is transferred to the liver for further metabolism. Other regulatory proteins, including Lecithin cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP) may regulate the CRT pathway (Ohashi et al., 2005). Therefore, it appears that dietary cholesterol may impact the activity of these proteins, resulting in higher cholesterol concentrations as well as larger HDL particles.

DIETARY AGENTS WITH CHOLESTEROL-LOWERING ACTIVITIES

Since dietary cholesterol may directly and/or indirectly elevate serum cholesterol levels, and thereby, increases the risk factors for some chronic diseases, including coronary artery disease,

attempts have been made to identify certain dietary agents with cholesterol-lowering effects. Cholesterol-lowering properties of several well-studied dietary agents are discussed below:

Plant sterols/stanols (phytosterols)

Among many dietary agents, plant sterols are well-known to inhibit intestinal cholesterol absorption. Plant sterols are very similar to cholesterol in their chemical structures. However, unlike cholesterol, they are not absorbed from healthy intestinal cells in animals or humans. The presence of adequate amounts of plant sterols in the intestinal lumen hinders cholesterol absorption significantly. There have been several mechanisms proposed for such inhibitory effects of plant sterols on cholesterol absorption. One original hypothesis is that plant sterols interact with cholesterol at the level of micelle formation (De Smet et al., 2012). Other potential mechanisms are interactions with enzymes and/or transfer proteins at the level of intestinal cells (De Smet et al., 2012). Overall, it has been documented that plant sterols at a dose of approximately 2 grams per day, consumed as part of healthy diets, may decrease LDL-cholesterol levels by approximately 13% (Moghadasian and Frohlich, 1999).

Evidence on overall safety and effectiveness of plant sterols has resulted in approval of health claims by both the Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA). The EFSA allows health claim to be marketed as ñplant stanols/sterols have been shown to lower/reduce blood cholesterolò. Similarly, the FDA statement reads as ñplant sterols as part of low-fat diets may reduce cardiovascular riskò. Health Canada also allows a health claim for plant sterols as ñPlant sterols help reduce (or help lower) cholesterolò (Health Canada, 2010b). Such approvals are the bases of the production of plant sterol-enriched food

products worldwide. These products include both solid foods as well as liquid beverages along with snacks. Available literature indicates that regardless of the type of food or beverage or the formulation of plant sterols (stanol vs sterols or free vs esterified), appropriate amounts of plant sterols can reduce serum cholesterol levels. However, it seems that the same dose of plant sterols through solid foods may be more efficient in cholesterol reduction than through liquid beverages. Furthermore, it seems that multiple daily doses may be more efficient than a single daily dose. Another factor that may modify the potency of plant sterols could be the base food. For example, consumption of plant sterols through fat spreads, mayonnaise, salad dressing, milk and yoghurt is more effective as compared to that through croissants and muffins, orange juice, non-fat beverages, cereal bars and chocolate.

Dietary fiber

Dietary fiber is another dietary agent with well established cholesterol-lowering activities (Brown et al., 1999). Dietary fiber exists in 2 major forms, namely soluble and insoluble fiber. Many studies have reported cholesterol-lowering activities for soluble fiber. Early studies did not differentiate among various sources of soluble fiber such as oats, guar gum and psyllium. However, a lot of attention has been paid to ϐ-glucan from oats (Ripsin et al., 1992). Similarly, ϐ-glucan from barely has also been shown to have cholesterol-lowering effects (Talati et al., 2009). This effect of ϐ-glucan led both the American and European authorities to approve health claims for oats and barely in regard to reducing serum cholesterol levels. Health Canada (2010c; 2012) also approved that oat and barely fibre helps reduce / lower cholesterol in blood.

Overall, one can conclude that consumption of approximately 3 grams of ß-glucan daily may reduce LDL-cholesterol and total cholesterol levels by 7%, and 6%, respectively (Harland, 2012). To receive 3 grams of ß-glucan from oats, for example, 84 grams of oats must be ingested. For some individuals, this may be a large amount and therefore, it may difficult to achieve the desired cholesterol-lowering effects from oats or barely. Whole grain products are another rich source of soluble fiber. Although epidemiological studies have reported an inverse association between consumption of whole grain products and cardiovascular disease (Mellen et al., 2008); it has not been established that whole grain fibers are the reason for this association. Pectin is another type of soluble fiber with established cholesterol-lowering effects. Fruits and vegetables are rich sources of dietary pectin. It has been suggested that consumption of 1 gram per day of pectin may reduce cholesterol levels by approximately 5 mg/dl (EFSA Panel on Dietetic Products; Nutrition and Allergies (NDA), 2010) However, unlike ß-glucan, there is no existing health claim for the cholesterol-lowering properties of pectin.

Soy protein

Cholesterol-lowering effects of soy protein have been long recognized. Several large clinical studies have suggested a reduction of up to 7% in LDL cholesterol concentrations after consumption of adequate amounts of soy protein (Anderson et al., 1995). These effects of soy protein are recognized as the ñintrinsicò effects, while the potential effect of replacement of other diet components, such as saturated fat, is considered an ñextrinsicò effect. One review article of 11 clinical trials reported the ñintrinsicò effect of soy protein on reduction of LDL cholesterol levels to be 4.3% (Jenkins et al., 2010). The ñextrinsicò effect of soy protein on LDL

cholesterol reduction was reported to be 3.6-6.0%. Therefore, one can calculate the total LDL cholesterol-lowering effects of soy protein to be the sum of ñintrinsicò and ñextrinsicò effects at 7.9-10.3% (Jenkins et al, 2010). Although no defined dose-response studies have been carried out for cholesterol-lowering properties of soy protein, a number of investigators suggest that an approximate intake of 25 grams of soy protein may be sufficient to produce significant cholesterol-lowering effects. This is the basis of health claims approved in both the USA and Europe indicating ñan intake of 25 grams of soy protein is associated with lowered blood cholesterol.ò This claim applies to foods containing at least 5-6.25 grams of soy protein per serving. Such foods may include soy milk, soy yoghurt, tofu, and meat alternatives (burgers, meatballs, sausages and mince).

Other dietary components

Several early studies have reported cholesterol-lowering effects for garlic products. For example, a study conducted on mildly hypercholestermic patients reported that consumption of 600mg garlic allicor was associated with significant reductions in both total and LDL cholesterol levels by 7-8% and 12-14%, respectively (Sobenin et al., 2008). On the other hand, another clinical trial reported no significant cholesterol-lowering effects for raw or powdered garlic or garlic extract at a dose of approximately 4 grams per day for up to 6 months. It appears that the cholesterol-lowering effects of garlic products may be influenced by several factors, including the formulation and the method of preparation.

Consumption of tree nuts may also reduce serum cholesterol levels (Kris-Etherton et al., 2008). In particular, consumption of almonds at an intake of 25-168 grams per day may result in a

significant reduction in both total and LDL cholesterol levels (Phung et al., 2009). Similarly, consumption of walnuts was reported to significantly reduce both total and LDL cholesterol concentrations (Banel and Hu, 2009). These studies provided strong enough evidence that both the European and American authorities approved a health claim stating, ñdata suggest, but did not prove, that the intake of 42 grams of nuts per day may reduce the risk of heart disease.ò

Flaxseed products also reduce both total and LDL cholesterol levels in humans (Pan et al., 2009). Flaxseed contains several beneficial phytochemicals, including ALA and lignin. Currently, it is not well-established that the cholesterol-lowering effects of flaxseed are due to ALA and/or lignin and/or other compounds. Saponins and flavonoids are among other dietary agents with reported cholesterol-lowering activities.

The cholesterol-lowering properties of the above-mentioned dietary agents were the basis for the formulation of the ñportfolio diet.ò This diet contains plant sterol, dietary fiber, soy protein and whole almonds. Several clinical studies reported that consumption of the ñportfolio dietò is associated with significant reductions in both LDL cholesterol levels and certain anti-inflammatory markers (Jenkins et al., 2005). **Table 2** summarizes cholesterol-lowering properties of dietary agents.

CHOLESTEROL METABOLISM

Both ñendogenousò and ñexogenousò cholesterol sources regulate the whole body cholesterol homeostasis. ñExogenousò cholesterol is derived from animal-origin food and can significantly impact the rates of synthesis and amounts of production of ñendogenousò cholesterol. Our knowledge on the absorption of dietary cholesterol is still limited. Several regulatory proteins,

receptors and/or transfer molecules play a crucial role in cholesterol absorption at the level of intestinal cells. Among those, Niemann-Pick C1-like 1 (NPC1L1), ATP Binding Cassettes G5 and G8 (ABCG5/G8), ABCA1, Liver X receptor (LXR), Acyl-CoA:*cholesterol* acyltransferase (ACAT), and CETP can be named.

NPC1L1 seems to play a key role in interactions between dietary sterols and the brush border membranes, and thereby facilitates sterol absorption. NPC1L1 has a sterol-sensing domain in its NH2 terminal which can bind to dietary cholesterol, transporting it inside the enterocytes. Abnormalities in NPC1L1 structure and function are associated with low cholesterol absorption in humans (Kim et al., 2013). In addition to intestines, several other tissues including the liver, ovary, lung and muscle express NPC1L1 mRNA in humans. This finding suggests that NPC1L1 may have other functions related to lipid homeostasis in humans; however, details of such functions are yet to be known. The fact that treatment with fenofibrate was associated with decreased cholesterol absorption in mice suggests that intestinal expression of NPC1L1 may be regulated through peroxisome proliferator-activated receptor α (PPARα) (Valasek et al., 2007). Furthermore, deletion of the gene for NPC1L1 in mice resulted in reduced cholesterol absorption (Davies et al., 2005).

Ex vivo experiments have shown that the bound sterol-NPC1L1 complex crosses the microvillus membrane to deliver cholesterol and plant sterols to the endoplasmic reticulum (ER) membrane. Once delivered to the ER, these sterols are esterified through the function of ACAT2. However, because ACAT2 has limited affinity for plant sterols, plant sterols will not be esterified and are therefore directed to the efflux pump ABCG5/G8 and returned back to the intestinal lumen for excretion. ABCG5/G8 also facilitates cholesterol excretion and thereby may reduce cholesterol

absorption. At least in mice, it has been reported that dietary plant sterols upregulate expression of ABCG5/G8 accompanied by reduced cholesterol absorption (Repa et al., 2002). Such findings were not observed in hamsters, indicating a tight species-related variation in intestinal sterol metabolism (Field et al., 2004). Over-expression of activated LXRα in the intestine of mice was associated with upregulation of ABCG5/G8 and ABCA1 transporters resulting in reduced cholesterol absorption and increased cholesterol efflux (Lo Sasso et al., 2010). The HDL receptor, scavenger receptor (SR)-B1 and multifunctional ligand receptor cluster of differentiation 36 (CD36) have also been proposed to have a role in cholesterol absorption. However, deletion of genes for these proteins in mice did not result in alterations in cholesterol absorption (Altmann et al., 2002).

Abnormalities in intestinal cholesterol homeostasis result in a number of diseases. For example, abnormalities in the ABCA1 gene are the molecular background for Tangier disease in which HDL particles are not made (Kang et al., 2010). It has been shown that an interaction between LXR and ABCA1 at the intestinal level regulates HDL formation. This suggests that dietary cholesterol absorption is required for ABCA1-LXR-mediated HDL formation by the enterocytes. Most likely, this mechanism is responsible for elevated HDL cholesterol levels following consumption of cholesterol-rich foods, such as eggs.

Another well-known abnormality in cholesterol metabolism is a lack of cholesterol synthesis. Almost all human tissues are capable of cholesterol synthesis. Among them, the contribution of the hepatocytes and enterocytes in the ñendogenousò cholesterol pool is significant. These cells can make 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) from acetyl CoA or acetoacetyl CoA. HMG CoA is further metabolized through HMG CoA reductase to produce downstream

molecules including mevalonate, farnesyl, squalene, and 7-dehydrocholesterol for formation of cholesterol. In Smith-Lemli-Opitz syndrome the conversion of 7-dehyrocholesterol to cholesterol is impaired. Therefore, subjects with this syndrome suffer from inadequate amounts of ñendogenousò cholesterol, but significantly benefit from ñexogenousò cholesterol.

Cholesterol is metabolized to bile acids by the hepatocytes through enzymatic reactions. In particular, the cholesterol 7-α hydroxylase and sterol 27-hydroxylase enzymes are responsible for bile acid production. Abnormalities in the production/function of these enzymes result in abnormalities in cholesterol catabolism. Cerebrotendinous xanthomatosis is the condition in which bile acids are not made; instead cholesterol is converted to cholestanol and bile alcohols. While bile alcohols are excreted through urine, cholestanol is accumulated in several tissues including the brain, tendons and lens. The most effective treatment for this condition is administration of bile acid chenodeoxy cholic acid (Moghadasian et al., 2002). **Figure 2** summarizes cholesterol metabolism and its various abnormalities.

COMMENTS

Approximately one-third of the body cholesterol pool comes from dietary sources. Foods of animal origin are the main dietary sources of cholesterol. Both ñendogenousò and ñexogenousò cholesterol are transferred by a number of lipoprotein particles including chylomicrons, VLDL, LDL and HDL. Elevated levels of LDL cholesterol and reduced levels of HDL cholesterol are independent risk factors for coronary artery disease. Several health authorities, including Health Canada and the American Heart Association, recommend intakes of dietary cholesterol to be <300 mg/day, and <200 mg/day for general population and cardiovascular patients, respectively.

Increased dietary cholesterol intakes result in increases in both HDL and LDL cholesterol levels. Therefore, the ratio of HDL/LDL cholesterol remains unchanged. Several studies have suggested considering the HDL/LDL ratio for assessing coronary artery disease risk. While considering such a recommendation, one may think that dietary cholesterol intake per se, may not significantly increase CAD risk. Furthermore, we now know that not all subjects respond to dietary cholesterol equally. Many large scaled clinical studies have identified ñhyper- and hypo-responderò people. Assuming that approximately 50% of the general population is ñhypo-respondersò, the impact of dietary cholesterol intake on risk for CAD becomes weaker. At the same time, the impact in ñhyper-responderò individuals can remain unchanged. In addition, dietary cholesterol may suppress synthesis of ñendogenousò cholesterol. Endogenous cholesterol is primarily made by the liver and secreted through VLDL particles; VLDL particles can be converted to LDL particles. On the other hand, dietary cholesterol is circulated primarily through chylomicrons, which can be metabolized to remnant particles and eventually picked up by hepatocytes for further metabolism. Such fine pathways may raise the question of the importance of the origin of cholesterol on atherogenesis. Since LDL particles and their oxidized forms are the primary lipoproteins in the pathogenesis of atherosclerosis, one may hypothesize that ñendogenousò cholesterol may be more atherogenic than ñexogenousò cholesterol. Such a hypothesis certainly needs to be tested through well-designed clinical and experimental studies. Furthermore, cholesterol supplementation is the main strategy in the treatment of Smith-Lemil-Optiz Syndrome. Thus, dietary cholesterol may save the lives of some individuals, while in others it may either be neutral or lead to increases in the risk for CAD, if consumed in excess.

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Table 1: Common sources of dietary cholesterol.

Animal	Food	Cholesterol Content (avg. per 100g serving)
Beef	Ground beef, extra lean, well done	78mg
	Brain, fried	1995mg
	Liver, fried	381mg
	Tenderloin, lean, broiled	78mg
	Animal Fat	109mg
Pork	Bacon, fried	113mg
	Brain, braised	2552mg
	Liver, fried	355mg
	Ham, cured, lean, roasted	55mg
	Animal Fat	95mg
Chicken	Breast or thigh, skinless, roasted	75mg
	Egg, whole, poached	364mg (approx. 2 large eggs)
	Egg yolk, cooked	119mg (1 yolk=17g)
	Liver, fried	564mg
	Animal Fat	85g
Fish/Seafood	Atlantic salmon, farmed, baked	63mg
	Walleye, baked	110mg
	Shrimp, boiled	195mg
	Snow Crab, boiled	71mg

	Lobster, boiled	72mg
	Lamb, forshank, lean, cooked	70mg
	Caribou, cooked	109mg
Other	Deer, roasted	112mg
	Bison, roasted	82mg
	Goose, meat only, roasted	96mg

Data obtained from The Canadian Nutrient File - Health Canada (2010a).

Table 2: Cholesterol-lowering efficacy of dietary agents

Dietary agent	Dose	Effects	Health Claim
Plant sterols/stanols	2 g/day	Approximately 10% reduction in LDL cholesterol levels	American and European health claims exists
db-glucan	3 g/day	Approximately 7% reduction in LDL cholesterol levels	American and European health claims exists
Soy protein	25 g/day	7-10% reductions in LDL cholesterol levels	American and European health claims exists
Tree nuts	42 g/day	Up to 5% reduction in LDL cholesterol levels	American and European health claims exists, but not conclusive
Flaxseed products	Not established	Not established	None
Garlic products	Not established	Not consistent	None
Saponins and flavonoids	Not established	Not established	None

Figure 1:

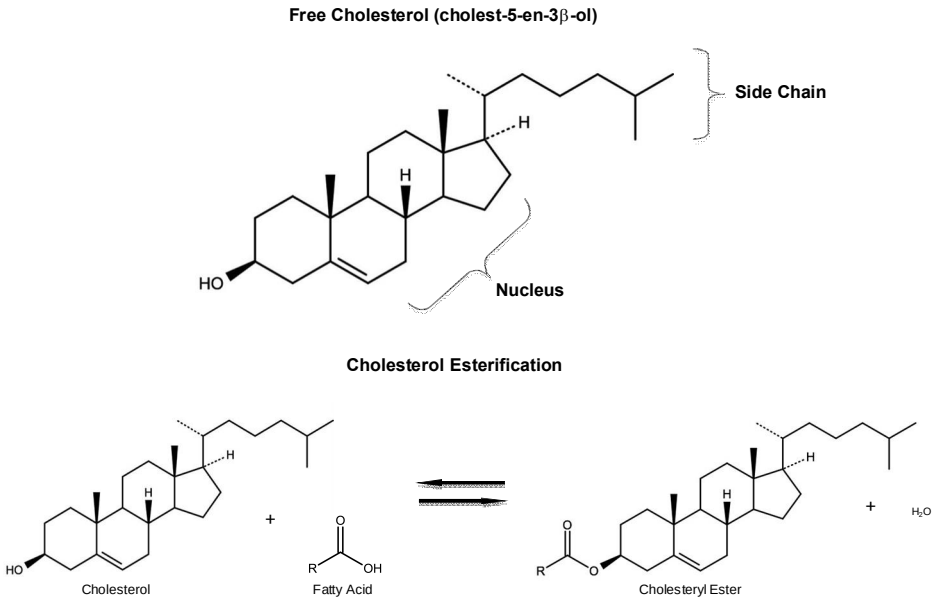

Figure 1: Chemical structures of cholesterol and cholestryl ester.

Although a number of fatty acids can be bound to cholesterol, medium to long chain fatty acids are common in cholestryl ester from animal products.

Figure 2:

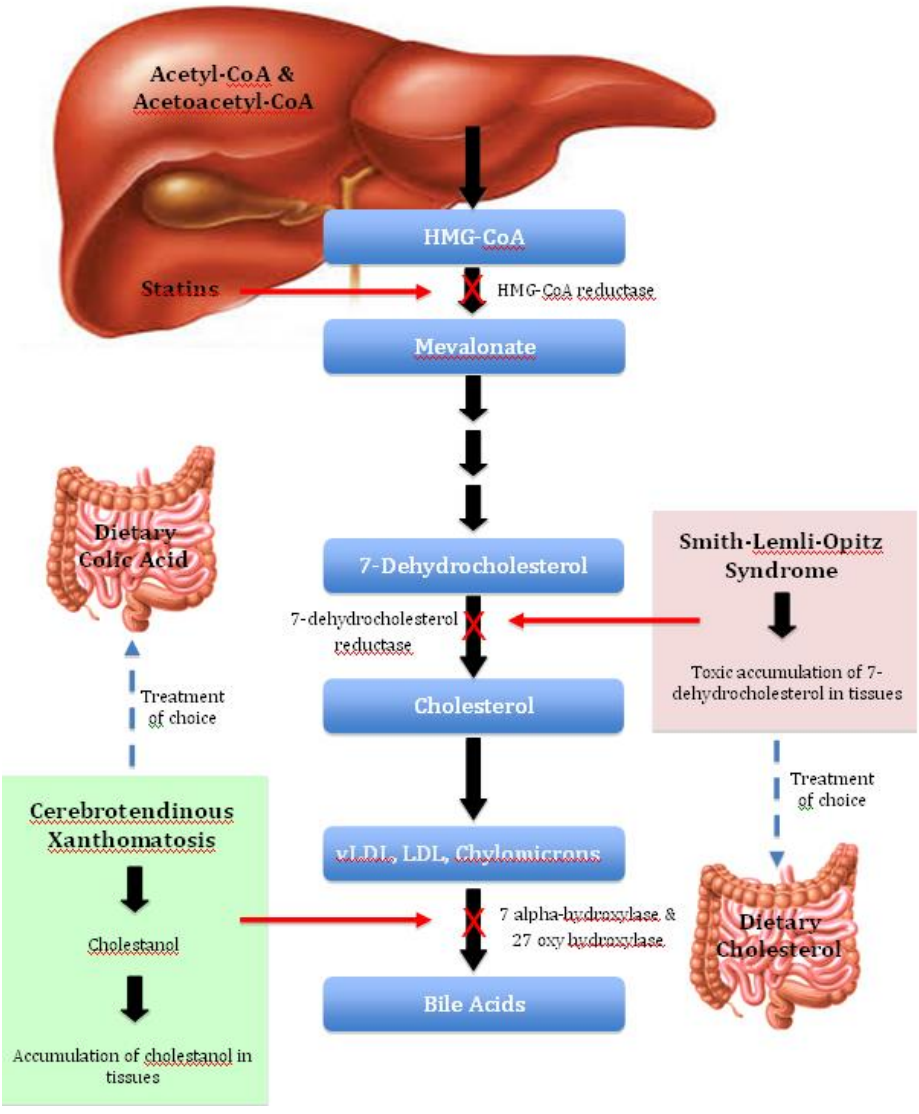

Figure 2: Synthesis of endogenous cholesterol by the liver is depicted.

HMG-CoA reductase is the rate limiting enzyme in cholesterol synthesis and statins are the common drugs to inhibit this enzyme. In Smith-Lemli-Opitz Syndrome cholesterol is not made due to a lack of enzyme and therefore dietary cholesterol is the main therapeutic approach. In cerebrotendinous xanthomatosis cholesterol is not converted to bile acid but to bile alcohol and cholestanol. Administration of bile acids is the primary therapeutic approach for cerebrotendious xanthomatosis.

