

## Association between Cholesterol Homeostasis with Intestinal Proteins, Enzymes and Drugs in Absorption of Cholesterol and its Relationship with Vascular Diseases: A Review

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### Abstract

The goal of this review is to discuss many aspects of cholesterol homeostasis in the body in order to presents the standards of cholesterol disposition and its levels, especially when several means might change the features of cholesterol synthesis and absorption and interrupt this equilibrium.

With the detection of pathways of cholesterol absorption and the discovery of different compounds that amend cholesterol absorption, there is a series of cholesterol lowering drugs, which may decrease the level of serum cholesterol by altering its absorption. It is recognized that the effects of cholesterol lowering drugs as well as genetics of a person, loss of body weight, enzymes and proteins may increase the cholesterol altering effect, but the impact of these agents on the mechanism of cholesterol homeostasis are poorly understood. The disturbance of cholesterol homeostasis is also related with vascular changes associated with cardiac and kidney problems.

Besides using different drugs and other means (plant sterol, enzyme, protein etc.), there is a need to improve the dietary pattern and life style. These may help to improve the cholesterol homeostasis.

**Keywords:** Cholesterol absorption; Activators; Inhibitors

### Introduction

Cholesterol is an oil-based substance. It is found in every cell of the body and has important natural functions. Cholesterol is a vital substance that is formed by the body but is also consumed from animal-derived foods. It is produced by foods that contain oil and fat. It is also synthesized in the liver [1].

### Dietary Source of Cholesterol and Consumptions of Calories

Cholesterol is found in animal foods include meats, poultry, fish, eggs, and milk products. According to Canadian Nutrient file the milk products are milk itself, ice cream, cheese (all varieties), milk shake used in routine. The cholesterol present in these milk products, give calories in ranges (ranges shows the variation of dietary source used) as follow:

One-cup milk containing cholesterol gives 21-26 calories, Half cup of ice-cream gives 83 calories, one and a half oz. cheese of all varieties gives 36-42 calories and one cup milk shake gives 27-40 calories.

Cholesterol present in meat and meat products including lamb, beef, chicken and fishes give calories as follow:

Two and half oz. lamb gives 36-99 calories, chicken gives 55-99 calories, and beef gives 53-96 calories. On the other hand two and half oz. liver chicken/lamb and liver of beef gives 310-423 calories and 266-297 calories respectively. Meat of fish and seafood gives 56-110 calories. The egg products give 179-193 calories.

### Significance of Dietary Sources of Cholesterol

Diet containing palm oil considerably increased total, LDL-, and HDL-cholesterol concentrations in comparison with vegetable oils that are low in saturated fat. Palm oil was also found to considerably increase HDL cholesterol as compared to trans-fat-containing partially hydrogenated vegetable oils [2,3].

Tea is a very popular beverage and is available in different forms like green, black and oolong tea. The catechins and the aflavins are polyphenols present in green and black teas. The animal studies show that these polyphenols prevent cholesterol absorption in intestine. Drinking green tea or green tea catechins lowers the serum cholesterol levels. The polyphenols hinder the micellar solubilization of cholesterol. The inadequate solubility of cholesterol by these polyphenols can be an important source of inhibition of cholesterol absorption [4].

Daily consumption of peanuts (46 g/d) over 24 week improved the nutrient profile of the diet (increased unsaturated fat,  $\alpha$ -tocopherol, niacin, and magnesium) and also improved the ratio of ratio of different lipids [1]. Major dietary sources of polar lipids are soybean, egg and marine lecithins [2]. Saturated Fatty Acids present in cheese and meat caused higher HDL-cholesterol and apo A-I concentrations. Cheese also causes a lower apoB: apo A-I ratio [5].

### Hazards of Dietary Sources of Cholesterol

Dietary cholesterol raises the vulnerability of low-density lipoprotein to oxidation, upsurges postprandial lipemia and potentiates the adverse effects of dietary saturated fat. Egg is one of the major source of dietary cholesterol and it increases

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the risk of coronary heart diseases by damaging the arteries [6]. Rates of cholesterol absorption differ extensively in the population from 25% to 80%, and average approximately 50% [7]. For an individual, the absorption rate seems to be persistent over time. In an individual, cholesterol is secreted into bile at the maximal rate of 2 g/day, consumed at rate of 0.4 g/day from diet and later absorbed at a rate of 50%, lost at 1.2 g/day in the feces. If such an individual also loses 0.4 g/day of cholesterol in the form of bile salts, the total loss of cholesterol would be 1.6 g/day (i.e., 25% as bile salts and 75% as cholesterol). The net daily production of cholesterol is equivalent to the amount of cholesterol lost in the feces minus the dietary cholesterol, which in this case totals to 1.2 g/day. This specifies that the quantity of cholesterol absorbed is equivalent to the amount lost (i.e., the body manufactures an amount approximately equal to the amount it absorbs) [8].

### Intestinal Cholesterol Absorption

Cholesterol balance is achieved by its synthesis in the body and by absorption in the gastrointestinal tract [8]. Cholesterol absorption occurs mainly in the duodenum and proximal jejunum that vary in different peoples [9]. Dietary and biliary cholesterol are the main sources for the intestinal absorption, which has roughly about 1/3 and 2/3 absorption, correspondingly [10]. There are two major stages of cholesterol absorption [11,12].

#### First stage of cholesterol absorption

The first stage is in the lumen and it engages digestion and hydrolysis of dietary lipids and tracked by solubility of cholesterol in mixed micelles containing bile acid/bile salts and phospholipids. Bile salts are secreted into bile at the rate of roughly around 24 g/day, but are produced at only a segment of this rate. The reason is because bile salts are recycled to liver from the ileum, where transporters present on the plasma membrane of the enterocytes in the distal region of the small intestine very competently take up bile salts (~98%) from the lumen and translocate them into the portal blood for return to the liver [13].

In addition to bile salts, cholesterol is secreted into bile at rates that vary up to 2 g/day. Within the intestine, biliary cholesterol mixes with cholesterol in the diet. Consequently, most cholesterol within the intestinal lumen is derived from internal sources via bile, whereas the diet contributes a relatively minor fraction. This process of solubilisation makes easy the cholesterol movement from the bulk stage of the lumen to enterocyte surface [14].

Hepatocytes very proficiently clear bile salts from the portal blood and re-secrete them into bile. The movement of bile salts between the liver and intestine is called the enterohepatic circulation. Although this process is extremely competent, 1–2% of bile salts spilled into the feces and escape recycling. This sums to a loss of approximately 0.4 g/day of cholesterol in the form of bile salt molecules. Within the liver, the conversion of bile salts to cholesterol occurs at a rate that accurately balances the loss into the feces. Bile salt sequestrants, such as colestevlam and cholestyramine, function to upsurge the fecal loss of bile salts. The liver responds by upregulating bile salt synthesis, and this ingests cholesterol within the liver [15].

#### Second stage of cholesterol absorption

In the second stage, cholesterol crosses the mucosal cell membrane by the processes of simple and facilitated diffusion. Thus, there is no need to any cholesterol transporter. In side of cell there is re-esterification of cholesterol is carried out. This esterified cholesterol is added into apolipoprotein containing lipoproteins that are secreted into the lymph [16,17].

### Factors Affecting the Cholesterol Absorption

Factors that give cholesterol-lowering affect by inhibiting the synthesis and absorption of cholesterol may be plant sterol, barley  $\beta$ -glucan, phospholipids, soluble fibers, phytosterols and a compound ezetimibe. On the other hand the hormone Cholecystokinin produced in G.I.T increases cholesterol absorption.

Plant sterols employ a hypocholesterolemic activity as it prevents intestinal absorption of cholesterol. As the sterol-solubilizing capacity of bile salt micelles was limited, plant sterols solubilized in micelles reduced the solubility of cholesterol. This might be the main reason of inhibition of cholesterol absorption by plant sterols [18].

A study demonstrated that the ingestion of barley  $\beta$ -glucan drops cholesterol by affecting the cholesterol synthesis, cholesterol absorption or bile acid synthesis. Results of this study indicated that improved bile acid synthesis rather than inhibition of cholesterol absorption or its synthesis could be accountable for the cholesterol-lowering effect of barley  $\beta$ -glucan [19].

Other studies experimentally proved that Phospholipids can impede intestinal absorption of cholesterol. Possible mechanisms that indicate inhibition of cholesterol intestinal absorption by phospholipids:

1. Additional Phospholipids hinders with effective micellar Phospholipids hydrolysis - a criterion for mucosal uptake of cholesterol.
2. Excess Phospholipids modifies the physicochemical properties of mixed micelles (i.e., their composition, size, and its natural characteristics) subsequent in reduced absorption of cholesterol.
3. Phospholipids has a direct effect on cellular cholesterol transporters that control intestinal cholesterol uptake [20].

Soluble fibers and phytosterols are the most potent substances that act as cholesterol absorption inhibitors. They are extensively used by the foodstuff production to improve the health-related stuffs of various food products. Their capacity to decrease intestinal cholesterol uptake leads to fall in the intestinal chylomicrons cholesterol content, transport of cholesterol to the liver decreased within chylomicron remnants, lower plasma levels of Low Density Lipoprotein-cholesterol (LDL-chol) and increased hepatic LDL-receptor movement. Decrease conversion of Very Low Density Lipoprotein, reduced liver Very Low Density Lipoprotein production and LDL also adds to lower Low Density Lipoprotein levels [21].

Also another factor that promotes cholesterol absorption is alkaline sphingomyelinase in the gut. This enzyme promotes cholesterol absorption by reducing dietary sphingomyelin levels in the intestinal lumen [22]. However it is reported that in humans, 1 g/day of dietary sphingomyelin does not change the blood lipid profile but causes an increase in High Density Lipoprotein -cholesterol concentration with no effect on cholesterol absorption and synthesis [23]. A compound, ezetimibe enhances the lipid profile in diabetic patients with dyslipidemia by reducing the cholesterol absorption [24].

In few cases, metabolism of bile acid might be affected (e.g., soluble fibers), that could be a mechanism for lowering of cholesterol. These compounds can be used as cardiovascular nutraceuticals and help to lower the Lower Density Lipoprotein -cholesterol levels in patients who are not able to touch their target Low Density Lipoprotein concentration [25].

Data from studies indicate that Cholecystokinin increases cholesterol absorption by activation of a pathway comprising CCK1R/CCK2R, Rab11a, G $\beta$  $\gamma$ , PI3K, Akt, and NPC1L [26].

### Physiological Factors Affecting Cholesterol Absorption in Intestine

Number of physiological and therapeutic factors affects cholesterol homeostasis, including: genetics of a person, circadian rhythm, body weight, enzymes, proteins ezetimibe, and statin therapy. However these factors shows a reciprocal link between absorption of cholesterol and its synthesis [27].

Genetic factors affecting cholesterol metabolism demonstrate an inverse relationship between two genetic vectors. These genetic vectors are the carriers of the isoform of apolipoprotein E or E2 and ATP binding cassette (ABC) or G8. The mutation of these variants causes a reduced absorption of cholesterol along with increased synthesis of cholesterol. Increased body weight indicates increase synthesis of cholesterol following with a reduction in the absorption of cholesterol. Loss of weight loss may decreased synthesis of cholesterol but has no effect on its absorption [27].

Therapeutic factors including stanols and plant sterols inhibit the absorption of cholesterol, but as a compensation increase its synthesis. Example is observed on case of Ezetimibe, that decreases the absorption of cholesterol from intestine with increase in synthesis of cholesterol. It also turn as the inhibitor of Niemann-Pick C1 protein and stops the formation of gallstone by decreasing the bioavailability of intestine-derived cholesterol to liver for biliary secretion. It also desaturate bile via the inhibition of intestinal cholesterol absorption [28].

Statin therapy reduces the synthesis of cholesterol and increases its absorption. These findings suggest that a change in one vector, consistently, results in a compensatory and opposing change in the other [29].

Orlistat restricts cholesterol absorption by the inhibition of NPC1L1 transport protein [30]. Berberine decreases the blood cholesterol levels by inhibiting the intestinal absorption and also by interrupting with intraluminal cholesterol micellarization and also by reducing the enterocyte cholesterol secretion and its uptake [31]. Evolocumab has a little effect on cholesterol synthesis and absorption regardless of significant Low Density Lipoprotein -Cholesterol lowering [32]. Pravastatin (PR) treatment reduced duodenal cholesterol transporter expression in mice. PR-induced increases in liver X receptor may be involved in reduction of Niemann-Pick C1-like 1 expression, lowers the intestinal cholesterol absorption [33].

Alkaline  $\alpha$ -sphingomyelinase help cholesterol absorption by decreasing the sphingomyelin levels in the intestinal lumen [22]. Niemann-Pick C1 Like 1(NPC1L1) protein plays a very important role in the absorption of intestinal cholesterol. NPC1L1 expression is augmented in small intestine and is present in the brush border membrane of enterocytes [34].

In addition, dietary sphingomyelin has perhaps valuable effects on diet-induced hepatic steatosis by decreasing the intestinal cholesterol absorption [35]. Numb, a clathrin adaptor is a pivotal protein for intestinal cholesterol absorption and is a target for hypercholesterolemia [36].

Further studies reveal that Anacetrapib (ANA) promotes pre  $\beta$  High Density Lipoprotein *in vivo* functionality, but has no effects on absorption of cholesterol [37]. Another study showed that the nonlipid

fraction of *Nostoc commune* var. *sphaeroides* Kützing, a blue-green alga exerts cholesterol and triglyceride lowering effects mainly by increasing hepatic fatty acid oxidation and by inhibiting intestinal cholesterol absorption [38].

A study proved that lycopene has inhibitory effect on the absorption of cholesterol in the intestinal cells. This inhibitory effect of lycopene is mediated, to some extent, by liver X receptor  $\alpha$ , Niemann-Pick C1-like 1 signaling pathway [39]. In a rodent model of metabolic syndrome, statin treatment poorly up-regulates intestinal lipid secretion because of increased intestinal cholesterol absorption. It also increases the intestinal expression of genes involved in lipid synthesis [40].

### Cholesterol Lowering Medications and Risk of Cardiovascular/Kidney Diseases

Disturbed cholesterol homeostasis is explained as towards reduced cholesterol synthesis and increased cholesterol absorption is associated with increased cardiovascular risk. Study showed that patients that has high cholesterol absorption mat not be helpful from treatment with statin, but could increase their cardiovascular risk when place on a drug that decreases endogenous cholesterol synthesis [41].

Hypercholesterolemia stimulates atherosclerosis due to increased intestinal cholesterol absorption which may effect on regulation of cholesterol homeostasis [42]. It is proposed that increase absorption of cholesterol followed by the increased circulating plant sterols that may facilitate the associations of ABCG8 and ABO variants (gene variants) with cardiovascular Diseases [43].

Results of another study indicate that variations in cholesterol homeostasis, low cholesterol synthesis and high cholesterol absorption, are related to high cardiovascular disease risk in a group of men and women with parallel plasma levels of Low Density Lipoprotein-cholesterol [44].

Patients with severe hypercholesterolemia can increase the renal injury. It is demonstrated that albuminuria and a decrease renal function indicate an increase serum campesterol levels (a cholesterol absorption marker) [45].

Stimulation of farnesoid X receptor (FXR) prevents intestinal cholesterol absorption by modulation of bile acid pool size and composition. It leads to increased reverse cholesterol transport (RCT). Targeting hepatic FXR and/or bile acids may be useful for improving reverse cholesterol transport, thus inhibiting the growth of atherosclerosis [46].

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