THE ROLE OF CHOLESTEROL IN ATHEROSCLEROSIS AND ITS POTENTIAL MANAGEMENT BY DIETARY FIBER

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Nearly 1,000,000 Americans die annually from cardiovascular diseases. A tremendous amount of current literature implicates increased cholesterol levels with an increased risk of atherosclerosis and coronary artery disease. For hypercholesterolemic patients, it has been determined that every 1% reduction in serum cholesterol results in a 2% reduction in the risk for coronary artery disease[1]. Consequently, pharmaceutical companies are formulating drugs that reduce cholesterol levels by a number of mechanisms, including: decreased absorption, decreased reabsorpotion of bile acids, decreased synthesis, and increased breakdown. However, a National Institute of Health (NIH) consensus panel recently recommended that a great majority of all Americans with hypercholesterolemic can be treated with diet therapy alone[2]. Since in most cases hypercholesterolemic is primarily dietary in etiology, the diet can be modified to successfully reduce cholesterol levels and avoid the expenses and potentially serious side effects of drug therapy. Towards this goal, the American Heart Association[3] recommends a diet in which the intake of total fat is lowered to approximately 30% of total daily calories. Special emphasis is placed on reducing calories from saturated fat to 10% and increasing calories from polyunsaturated and monounsaturated fats to 10% each. Also recommended is an increase in complex carbohydrates intake by up to 60% of total daily calories and limiting cholesterol intake to no more than 300 mg per Day. Strict compliance with the American Heart Association diet has been associated with reducing cholesterol levels by 10%[4]. However, the addition of water soluble dietary fibers to such a regimen can reduce cholesterol levels up to 30% with a concomitant theoretical decrease of 60% in risk of coronary heart disease [5-10].

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Definition of Dietary Fiber

Dietary fiber consists of the endogenous components of plants ingested as food that are resistant to the action of the digestive enzymes released in the alimentary tract of man. Non-starch polysaccharides and lignin are the chief constituents of dietary fiber. The heterogenous mixture of substances comprising dietary fiber can be divided into two groups: 1) water-soluble fibers, which include certain hemicelluloses, gums, pectin, and storage polysaccharides often found in legumes, fruits, barley and oats and; 2) water-insoluble fibers which include cellulose, many hemicelluloses, and lignin often found in many grains (e. g., wheat) and vegetables.

These two categories of dietary fiber have somewhat different physiological effects[11]. Soluble fibers delay gastric emptying, decrease serum cholesterol levels, slow glucose absorption, increase small and decrease large intestinal transit time. In contrast, insoluble fibers decrease intestinal transit time, delay starch hydrolysis and increase fecal bulk, while also slowing glucose absorption.

Dietary fiber has remained for a long time a neglected component of food probably because of its relatively negligible nutritional value. However, recently, the important and multifaceted role that dietary fiber plays in good health maintenance is being redefined. Among its many beneficial effects, a prudent diet rich in dietary fiber has been shown to lower serum cholesterol values and thus reduce the risk of atherosclerosis and associated sequelae (vide infra).

Cholesterol Biosynthesis

Cholesterol serves as the precursor for all steroid hormones, modulates the fluidity of cell membranes, and is necessary for the formation of bile salts[12]. The human body's two sources of cholesterol are dietary and de novo synthesis. Cholesterol is principally synthesized by the liver,

with appreciable amounts by the intestines, and lower levels produced by the ovaries, tests, and adrenal glands. All the synthetic reactions occur in the cytoplasmic compartment of the cell and most of the required enzymes are located in the endoplasmic reticulum. Three 2 carbon acetyl CoA units are sequentially condensed in two enzymatic steps to form the 6 carbon compound 3-hydroxy 3-methyl glutaryl CoA (HMG CoA) (fig 1). HMG CoA is then reduced by the action of HMG CoA reductase to form mevalonic acid, which is the rate determining step of cholesterol biosynthesis. Five mevalonic acids are needed for cholesterol formation. Mevalonic acid is enzymatically phosphorylated to form 3-phospho 5-pyrophospho mevalonate that is in turn converted to the 5 carbon isopentenyl pyrophosphate via a decarboxylation and dephosphorylation. Is opentenyl pyrophosphatecan isomerize to form dimethylallyl pyrophosphate. In several enzymatic steps 2 isopentenyl pyrophosphates and a dimethyllyl pyrophosphate are condensed to form the 15 carbon farnesyl pyrophosphate. Next, 2 farnesyl pyrophosphates are condensed yielding the 3o carbon linear squalene. In several enzymatic steps squalene is cyclized, reduced, and demethylated to form the 27 carbon compound cholesterol.

A normal healthy adult on a low-cholesterol diet consumes about 0.3 grams of cholesterol per day and in addition, endogenously synthesizes another 0.8 grams of cholesterol per day[12]. The rate of endogenous synthesis is partly regulated by the level of dietary intake of cholesterol. Dietary cholesterol inhibits the activity of HMG CoA reductase in the liver and also suppresses the synthesis of this enzyme. Furthermore, intracellular free cholesterol activates acyl CoA-cholesterol acyl transferase, an enzyme that catalyzes the formation of cholesterol esters which accumulate in storage droplets.

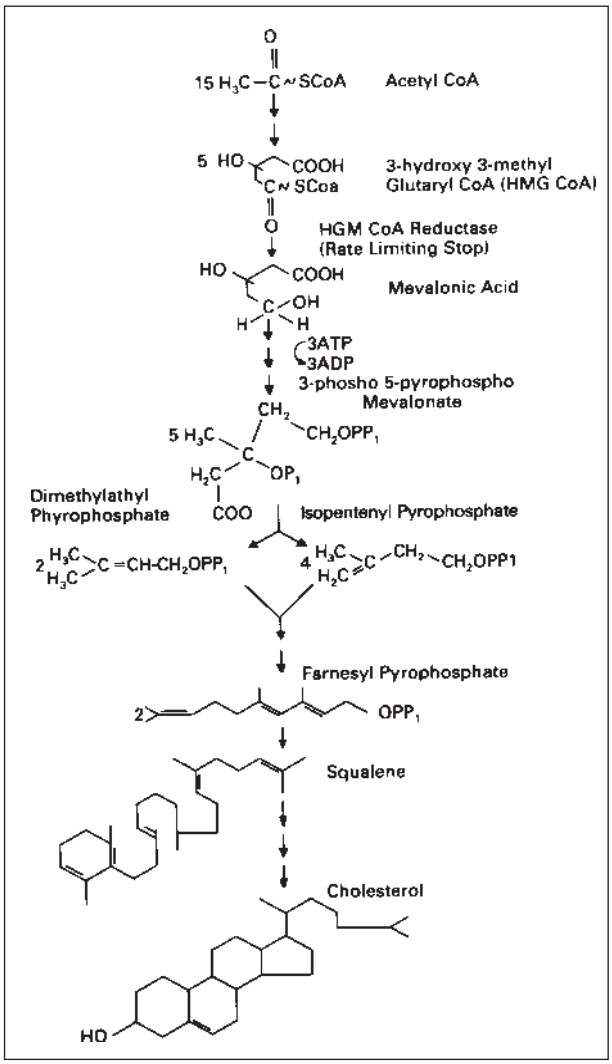

Fig. 1 - Biosynthetic pathway for cholesterol

Enterohepatic Circulation

Cholesterol is broken down by hepatocytes to form primary bile acids which comprise approximately 50% of the dry weight of bile (fig 2)[13]. Bile acids are conjugated to either glycine or taurine to form bile salts and are then released to the gall bladder to be concentrated and stored between meals with the other components of bile, including some free cholesterol. During meals bile is released from the gall bladder through the common bile duct to the small intestine where it acts to emulsify dietary lipid thus aiding absorption of lipid in the duodenum, jejunum, and proximal ileum.

Secondary bile salts are formed by the action of intestinal bacteria on primary bile salts. Bile acids are reabsorbed in the terminal ileum by secondary active transport or simple diffusion, bound to plasma proteins, and returned to the liver via the hepatic portal circulation. Once inside the liver, bile acids are rehydroxylated, reconjugated, and recycled to the intestine bypassing the gall bladder. Hepatocytes are very efflcient at extracting bile acids from the blood and the bile may be resecreted three to four times during and extended meal. The most important signal governing th synthesis and secretion of bile acids is the rate of return of bile acids to the liver[13]. During meals, bile acids in the portal blood stimulate the secretion of bile acids, but inhibit bile acid synthesis. At times when the level of bile acids in the portal blood is low, such

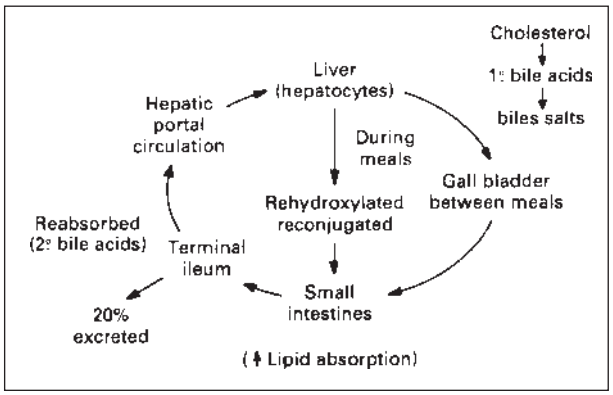

Fig. 2 - The enterohepatic circulation

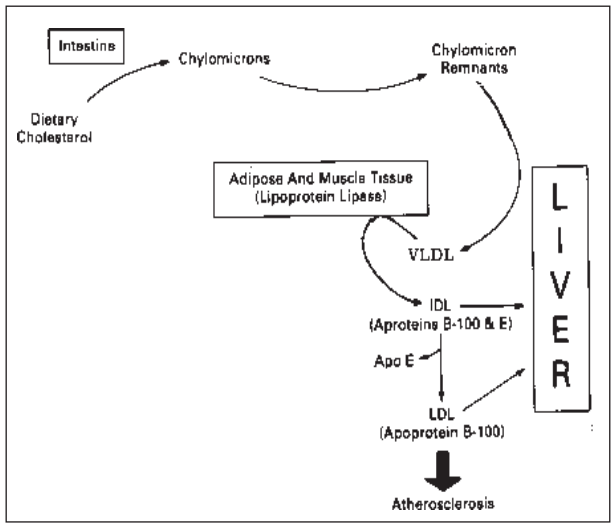

Fig. 3 - The exogenous and endogenous cholesterol transport system

as in between meals, bile acid synthesis attains near maximal rates.

Approximately 20% or less of bile acids are excreted daily in fecal matter and this represents the body's only method to dispose of cholesterol.

Low Density Lipoprotein Receptor Hypothesis

The exogenous fat transport system begins when dietary cholesterol and fat are absorbed by intestinal mucosa to be packaged into lipoprotein particles consisting of cholesterol esters and triglycerides called chylomicrons (fig. 3)[14]. Chylomicrons enter the bloodstream, and in the capillaries of adipose and muscle tissue, lipoprotein lipase liberates fatty acids from the chylomicrons to replenish local tissue supplies. The cholesterol rich chylomicron remnants bind specific receptors on hepatocytes that mediate their uptake and removal from the circulation.

Once inside the hepatocyte, cholesterol is extracted from the chylomicron remnant and severs as a readily available intracellular store for needs such as bile acid synthesis and incorporation into cell membranes. Some of the cholesterol is repackaged into very low density lipoprotein (VLDL) particles that primarily consist of a core of triglycerides mixed with a lesser amount of cholesterol ester, which is surrounded by a coat of phospholipid and unesterified cholesterol with two surface proteins embedded inthe coat known as apoprotein B-100 and apoprotein E. The release of VLDL into the circulation by hepatocytes marks the start of the endogenous fat transport system.

As the VLDL particle enters the microcirculation of fat and muscle tissue, once again a significant portion of its triglyceride content is removed, leaving a particle enriched in cholesterol esters that maintains its two surface markers and is known as intermediate density lipoprotein (IDL). Within six hours, approximately 50% of the newly formed IDL is taken up by the liver via receptor mediated endocytosis to be reutilized. With time, apoprotein E dissociated from the surface of IDL particles remaining in the circulation, leaving a new particle termed low density lipoprotein (LDL) that bears apoprotein B-100 as its sole surface marker. Since LDL receptors display a higher affinity for apoprotein E than apoprotein B-100, LDL particles have a longer circulating half-life than HDL particles.

The number of LDL receptors displayed on a cell's surface varies directly with that cell's need for cholesterol. This occurs by a negative feedback system whereby increasing intracellular stores of cholesterol down regulate the number of cell surface LDL receptors. Therefore, in the face of adequate intracellular supplies of cholesterol, increased dietary intake of cholesterol is associated with increased levels of circulating LDL. The LDL receptor hypothesis states that a substantial proportion of atherosclerosis in the general population is attributable to dangerously high circulating levels of LDL, resulting from excessive cholesterol intake in proportion to the quantity of LDL receptors necessary to lower this burdens[14].

Pathogenesis of Atherosclerosis

Atherosclerosis is a disease process that specifically affects the intima of large elastic and large and medium-sized muscular arteries. Histologically, the basic lesion – the fibrous plaque

or atheroma – consists of a fibrous cap on the luminal surface; a variable admixture of lipidloaded smooth muscle cells and macrophages; an accumulation of connective tissue including collagen, elastic fibers, and proteoglycans; and a core of extracellular lipid-rich deposits. Lipid is a constant and characteristic component of fibrous plaques, although its amount varies greatly amongst lesions. The lipid is primarily cholesterol and cholesterol esters. Since both apoprotein B and LDL have been isolated from atherosclerotic lesions it is obvious that the cholesterol content of atheromas is derived from plasma lipoproteins.

The exact pathogensis of atherosclerosis is presently unknown, but a number of theories have been proposed to account for its etiology. The "imbition (insudation, infiltration) theory[15,16] suggests that atherosclerosis is due to an accumulation of fats in the intima that are derived from high levels of circulating lipoproteins and that cellular proliferation in the intima is a low grade inflammatory reaction to this increased filtration of lipid. The "hemodynamic theory" proposes that since atherosclerosis is associated with large arteries and hypertension, and plaques tend to develop at sites of turbulence or disturbed blood flow, atherosclerosis may be able to be explained on a hemodynamic basis. The "encrustation or thrombosis theory"[16] postulates that following focal endothelial injury small aggregates of platelets, fibrin, and leukocytes form a small thrombus over the site of injury that grows and organizes with time eventually resulting in plaque formation.

The "response to injury hypothesis"[17/19] incorporates aspects of the encrustation and imbition theories and states that atherosclerosis is initiated in response to some form of injury to the arterial endothelium.

Risk factors for endothelial injury include hypertension and cigarette smoking, but it remains a possibility that by unknown mechanisms chronic hyperlipidemia itself may initiate endothelial injury[20, 21]. Platelets and monocytes attach to the injured area and promote smooth muscle proliferation in the intima most likely in response to platelet derived growth factor (PDGF)[22]. Smooth muscle cells then synthesize and elaborate the connective tissue components of the plaque. Plasma lipid infiltrates the lesion and may accumulate extracellularly or since PDGF increases the number of LDL receptors os smooth musole cells[22], the cholesterol can also accumulate intracellularly.

Other theories suggest that high levels of circulating LDL may become chemically modified, diffuse across the endothelial barrier due to a concentration gradient, and collect within smooth muscle cells and macrophages independent of the LDL receptor, and therefore accumulate to excessive levels intracellularly not subject to feedback inhibition[23-26]. Still other theories postulate that the primary event in atherosclerosis may be a defect in smooth muscle cells[27] or growth control mechanisms[28] for smooth muscle cells that lead to uncontrolled proliferation. That each of the aforementioned theories appears to correlate with some aspect of the atherosclerotic process, but that none fully accounts for its pathogenesis seems to confirm the notion that atherosclerosis is of complex and multiple origins.

Despite uncertainty about its etiology, much more is known about the complications of atherosclerosis. Presently, approximately 50% of all deaths in the United States are attributed to atherosclerosis related diseases[29]. The plaque gradually grows with time, which creates an increasing impediment to luminal blood flow. This may lead to ischemia, and since the coronary and cerebral arteries are prime targets for atherosclerosis, myocardial infarction or cerebral infarcts may result.

The growing plaque may also cause pressure atrophy of the media, leading to weakening of the vessel wall and eventual aneurysm. Also, surface ulceration of the plaque may lead to thrombosis that further compromises lumenal diameter or may result in embolism. Finally, with time these atherosclerotic plaques will calcify.

Clinical studies linking LDL levels with risk of cardiovascular disease

Several large scale, long-term clinical trials conducted during the past two decades have made clear the association between elevated serum cholesterol levels and increased risk for cardiovascular disease, especially coronary heart disease (CHD). The Framingham Heart Study shows that there is a direct correlation between CHD and serum LDL concentration, and an inverse correlation between serum HDL concentration and CHD[30].

Data from the NHLBI Type II Coronary Intervention study indicate that decreases in LDL and total cholesterol (TC), and increases in HDL/TC, and HDL/LDL ratios as achieved by diet therapy and cholestyramine were effective in

delaying the progression of coronary artery disease in 143 hyperlipidemic men studied[31]. In the Lipid Research Clinics – Coronary Primary Prevention Trial (LRC-CPPT), 3.806 hypercholesterolemic men were placed into placebo or cholestyramine receiving groups and subsequently monitored for an average of 7-10 years1,[32]. The LRCCPPT presented convincing clinical evidence that lowering serum cholesterol decreased the incidence of myocardial infarctions, and that each 1% reduction in cholesterol results in a 2% reduction in the risk for CHD. The Helsinki Heart Study demonstrated that using gemfibrozil to reduce total and LDL cholesterol, while concomitantly increasing HDL cholesterol, decreased the incidence of CHD in high risk asymptomatic men when compared to placebo[33]. Finally, the Cholesterol Lowering Atherosclerosis Study (CLAS) showed that after coronary artery bypass surgery, the use of drugs to aggressively lower patients' LDL levels and also increase HDL levels exerted a beneficial effect (i. e., reversal or retardation of atherogenesis) on both native coronary arteries and venous bypass grafts, when compared to placebo treated controls[34]. The results of these clinical trials and others have been reinforced by morphometric studies of atherosclerotic plaques at human autopsy and experimental animal models of atherosclerosis.

Epidemiological studies linking decreased dietary fiber and increased incidence of cardiovascular disease

Epidemiologic studies of mortality rates from cardiovascular disease in different countries indicate that dietary fiber may play a protective role. Within populations of common lineage, living in different environments and cultures, populations with a large intake of fiber have a lower relative risk of death from cardiovascular disease than similar populations with lower dietary levels of fiber. For example, the prevalence of ischemic heart disease is higher among American Blacks than African Blacks[35,36]. Similar trends have been noted between Japanese immigrants to Hawaii and native Japanese[37], as well as between New Zealand Maori populations and less westernized Polynesian Island peoples[33]. In all of these instances, the switch to a more westernized diet with its associated lower fiber content appears to predispose to a greater incidence of CHD, secondary to increased serum cholesterol levels[39,40].

In a retrospective study, the British Department of Health and Social Security attempted to explain the marked increase in mortality from ischemic heart disease (IHD) among British people, during the period 1900 to 1970[41]. The study revealed that starchy foods, including associated fiber, in the diet had decreased markedly from 1860 to 1910 and continued to decline from 1910 to 1970, while during this same time period the fat content of the diet increased. They concluded that "populations who eat a diet rich in fiber usually have a lower serum cholesterol, and a lower mortality from IHD than those who eat a western-type diet"[41].

In two separate studies, one in England[42] and the other in the Netherlands[43], it was noted that mortality from CHD was more prevalent in men with low levels of dietary fiber intake than in men with higher levels of it. This same inverse relationship between fiber intake and CHD mortality rates was reported to be significant in a study of levels of dietary fiber intake versus CHD mortality rates for people in 20 developed countries[44]. Rankings of the countries revealed that Japan had the highest fiber intake and the lowest level of CHD, whereas the United States had the lowest fiber intake and the highest levels of CHD.

A prospective study of 1,001 middle-aged men of Irish descent revealed that those who died of CHD had higher dietary intakes of cholesterol and saturated fat and lower intakes of dietary fiber in comparison to their living counterparts[45].

It should be noted that in the aforementioned studies dietary fiber in general was the variable reported and not specific types of fiber.

Therefore, it remains a possibility that the reduction in the rate of CHD in association with dietary fiber intake may be independent of serum cholesterol concentration especially if the bulk of the fiber intake was wheat, which has little effect on serum cholesterol levels[42].

Clinical investigations linking increased dietary fiber intake and decreased cholesterol levels

In 1975, Jenkins et al[46] reported the findings of a study aimed at determining the effects of several different fibers on serum cholesterol concentrations. For a period of two weeks, they supplemented the regular diet of healthy volunteers with 36 g per day of either guar gum, pectin, or wheat fiber and then compared subject's serum cholesterol concentrations following the trial period to pre-study baseline values. The

guar and pectin groups experienced a significant hypocholesterolemic response, while the wheat group showed an insignificant increase in serum cholesterol. In another study, the normal diets of healthy college students were supplemented with 50 g per day of either oat bran or wheat bran in the form of a muffin for a period of six weeks[47]. At the conclusion of the study, those students receiving oat bran supplementation showed a 12% decrease in serum cholesterol, whereas the wheat supplement group revealed no significant change in serum cholesterol concentration. Based on the results of these studies and others, it has been concluded that soluble fibers have hypocholesterolemic effects while insoluble fibers do not.

Investigators then began to detemine whether dietary fiber supplementation was therapeutic for patients with high serum cholesterol concentrations. Jankins et al[48] supplemented 15 g of guar gum daily into the usual diet of patients with type IIa or IIb hyperlipidemia. At the conclusion of the 2-week study period, an average 10% decrease of serum cholesterol was noted with no significant change in serum triglyceride levels[48]. In another study of patients with either type IIa or IIb hyperlipoproteinemia, Kirby et al[49] randomly assigned patiens in a metabolic ward to one of two diets, each being identical in energy content and dietary composition, but differing in that one diet contained 100 g of oat bran per day. At the end of 10 days patients were crossed over from one dietary regimen to the other. At the conclusion of the study, it was noted that while on the oat bran, supplemented diet patients significantly reduced total serum cholesterol levels by 13% with a 14% reduction in LDL cholesterol when compared to control (without oat bran) diets[49]. HDL cholesterol levels were similar in both groups. In a similar metabolic ward study, Anderson et al[50] successfully lowered total serum cholesterol by 19% and LDL cholesterol by 23% without significantly affecting HDL cholesterol values in hypercholesterolemic men versus controls. This was a 3-week experimental period, in which the patients' diets were supplemented with 100 g per day of either oat bran or beans. In order to assess more longterm effects of bean bran or oat supplementation, Anderson et al[7] instructed hypercholesterolemic men to supplement their high carbohydrate diets with 50 g (one half to one cup) per day of either oat bran or cooked dried beans. After a 24-week follow-up period, patients were noted to have an average 26% decline in total serum cholesterol and LDL cholesterol values were 24% lower than baseline[7]. Several of the patients were followed for 99 weeks, and at the conclusion of this period total serum cholesterol values were on the average 22% lower, LDL cholesterol was 29% lower, HDL cholesterol was 9% higher than initial values, and compliance with the diet was high[7].

Dietary supplements of soluble fiber have been found to improve glycemic control, increase insulin sensitivity, and lower serum cholesterol levels in diabetic patients. Jenkins et al[51] supplemented the diets of lean diabetic patients with 13 g of guar gum daily, incorporated in crisp bread. At the of the experimental period, patients had significantly reduced total serum cholesterol by 13%, while the HDL, fraction remained unchanged[51]. In a more long-term study, lean diabetic subjects incorporated 14-26 g of guar gum in crisp bread into their daily diet, and at the conclusion of a 6-month experimental period were noted to have reduced LDL cholesterol by 15%, while HDL cholesterol remained unaltered[52]. Ray et al[53] reported a 30% drop in total serum cholesterol after incorporating guar gum into the diets of obese diabetic patients.

High-fiber, high-carbohydrate (HCF) diets that contain large amouns of complex carbohydrates, supplemented with fiber and including low levels of cholesterol, have also been shown to improve glycemic control and decrease insulin requirements in diabetic subjects. Anderson and other investigators have noted that such HCF diets lowered total serum cholesterol by 30% in type I and 24% in type II diabetics during a 3-week trial period[6,54,55]. It was also observed that the HCF diet lowered serum triglyceride levels by 15%[6]. The Uppsala Primary Preventive Study documented that elevated serum triglyceride levels are an independent risk factor for coronary artery disease[56]. In 1980, Gould et al[57] reported that incorporating 100 g of oat bran into a HCF diet decreased total serum cholesterol by 38%, lowered the LDL cholesterol fraction by 58%, and increased HDL cholesterol by 82% in the four diabetic patients studied. Longterm studies of lean diabetic patients adhering to a modified HCF diet for outpatient studies, has revealed an average decrease in total serum cholesterol of 15% in comparison to initial values after 4 years[58].

Including soluble fiber in traditional highfat, Western-type diets has also benn shown to significantly decrease serum cholesterol. In 1981, Kirby et al[59] reported the results of supplem-

enting the usual diets of hypercholesterolemic men with 100 g oat bran daily. Theyr daily diet also included 430 mg of cholesterol, but at the end of a 3-week experimental period total serum cholesterol was reduced by 13% and LDL cholesterol reduced by 14% in comparison to pre-study values[59].

Cholesterol lowering value of selected fibers

The following is a sampling of studies on sspecific soluble fibers that have been shown to decrease serum cholesterol values in man (table I)

Oats – Oat bran is rich in the β–glucan oat gum, which is believed to be the ingredient responsible for its cholesterol lowering action. While feeding 125-140 g of rolled oats to healthy subjects, researchers have noted a decrease in total serum cholesterol from 8 to 11% [60,61]. In 1980, Gould et al[57] reported that oat bran selectively lowered serum LDL cholesterol, while concomitantly raising HDL cholesterol. These findings have been confirmed by Roth and Leitzmann[62] while studying subjects who ate oatmeal for breakfast. In both short[50] an long-term[7] studies, Anderson et al have significantly reduced serum cholesterol levels in hypercholesterolemic subjects. Oat bran seems to be quite palatable, being found in many common foods such as cereals and breads, and is associated with few serious side effects. By incorporating more oat bran products into the diet, specific soluble fiber sipplements can be avoided and thus long-term patient compliance is increased.

Guar Gum – Guar gum is a galactomannan storage polysaccharide from the cluster bean, which in dilute aqueous solutions forms an extremely viscous gel. Many groups have reported hypocholesterolemic effects with a guar gum dietary supplementation in both short - and long-term studies of normal[46], diabetic[51,42], and hypercholesterolemic subjects[48]. Guar gum appears to solely lower the LDL cholesterol fraction, while HDL cholesterol remains unchanged. Approximately 20 g of guar gum daily seems to lower total serum cholesterol by 11%[63]. Ingested raw guar gum, hydrated or not, is usually quite unpalatable and may lead to a variety of gastrointestinal symptoms including feelings of fullness, diarrhea, nausea, vomiting, and abdominal pain[64]. Formulation to make guar gum more palatable such as incorporation in crisp bread[52], processing[65], or including an inhibitor to prevent gelation have been met with varying degress of acceptance by patients.

Psyllium – A hydrphilic mucilloid extracted from the outer epidermis of dried ripe seeds, Plantago ovata (Blond Psyllium), has been used for a number of years as a bulk laxative for the treatment of chronic constipation. Since psyllium extract has been determined to be rich in soluble fiber, a number of studies have been carried out to investigate its effectiveness to lower serum cholesterol. In 1995, Garvin et al[67] showed that the addition of psyllium colloid to the diet

TABLE I – Sample studies demonstating the hypocholesterolemic effect of dietary supplementation with selected fibers*l

Insoluble Fiber Source	Type of patients studied (weeks)	Duration of study	Dose (g/day)	Mean percents change in serum lipids: Total cholesterol	LDL	HDL	Triglycerides
Dried bean[50]1º	Hypercholesterolemic men	3	115	↓19%	↓23%	↓13%	↓3%
Guar gum[116]	lº Hypercholesterolemic men & women	8	16	↓11%	↓10%	↓5%	↓22%
Locust gean gum[82]	1º Hypercholesterolemic men, women & children	8	adults 25 children 15	↓10-17%	↓11-19%	↓7-9%	↓10%
Oat bran[50]	1º Hypercholesterolemic men	3	100	↓19%	↓22%	↓6%	↓19%
Pectin[78]	Healthy young men & women	3	15	↓15%	–	–	↑ 1%
Psyllium[69]	Mild-moderate hypercholesterolemic men	8	10.2	↓15%	↓20%	↓6.5%	↓13%
Soybean polysaccharide[71]	Mild-moderate hypercholesterolemic men & women	4	25	↓11%	–	↓9%	↑17%
Xanthun gum[83]	Type II diabetics men & women	6	12	↓7%	↓13%	↓2%	↑ 1%

LDL – low density lipoprotein; HDL – ligh density lipoprotein.

* Patients in the these studies may have also undergone dietary and exercise modification that may be in part responsible for cholesterol lowering effects.

- Values not reported in journal article

of normal male medical students significantly lowered serum cholesterol. Later, Lieberthal and Martens[68] were able to achieve a 14% decrease in serum cholesterol concentration of hypercholesterolemic patients given similar doses of psyllium for a 5-week experimental period. In a similar study, Anderson et al[69] supplemented the daily diets of hypercholesterolemic men with 3,4 g of psyllium. Following an 8-week experimental period, they successfully lowered total serum cholesterol by 15% and LDL cholesterol by 20% in hypercholesterolemic patients and noted that these reductions became progressively larger with time[69]. Danielsson et al[70] supplemented the normal diets of patients with essential hyperlipoproteinemia with approximately 10 g of psyllium per day for periods up to 29 months, and noted an average decrease in serum cholesterol of 17%. Over-the-counter psyllium mucilloid preparations (e.g., Liberally®) have been commercially produced to achieve good consumer acceptance, which decreases the incidence of adverse effects and thereby increases compliance.

Soybean – Polysaccharide extracted from soy beans with its major hemicellulose contituents of arabinoglycans has been postulated to have hypocholesterolemic properties. Shorey et al[71] reported lowering total serum cholesterol by 11% in hypercholesterolemic subjects taking 25 g of soybean polysaccharide for a period of 8 weeks in a crossover study. However, several other researchers[72,74] have failed to document lowering serum cholesterol include: pectin[75,80], mentation with soybean polysaccharide extracts. Therefore, the hypocholesterolemic value is uncertain and further studies are needed.

Other soluble dietary fibers implicated in lowering serum cholesterol include: pectin[75-80], gum arabic[81], locust gum[82], xanthum gum[83], and bean products[50,84].

Potencial adverse effects

In general, most adverse effects associated with fiber supplementation are mild and disappear following removal of the fiber from the diet. Fiber may decrease the availability of certain minerals[85]. However, a moderate level of fiber intake does not appear to detrimentally alter mineral balance, and there may be adaptation to any alteration in mineral availability caused by increased dietary fiber intake[86]. The major side effects associated with some soluble fibers are the various gastrointestinal disturbances brought on by the bulking properties of some fibers.

Proposed mechanism of action

Soluble dietary fiber binds bile acids and cholesterol in the small intestine and decreases reabsorption in the terminal ileum (fig 4). Therefore, more bile acids reach the colon for excretion in the feces and a lower concentration of bile acids returns to the liver via the enterohepatic circulation. This serves as a signal for increased bile acid synthesis. As hepatocytes catabolize cholesterol to make bile acids, the concentration of cholesterol falls within the cell. The rates of synthesis of LDL receptors are inversely correlated with the amount of cholesterol in cells. Thus, more LDL receptors are expressed on the surface of hepatocytes, more LDL is brought into the cell by receptor mediated endocytosis, and plasma LDL concentrations fall.

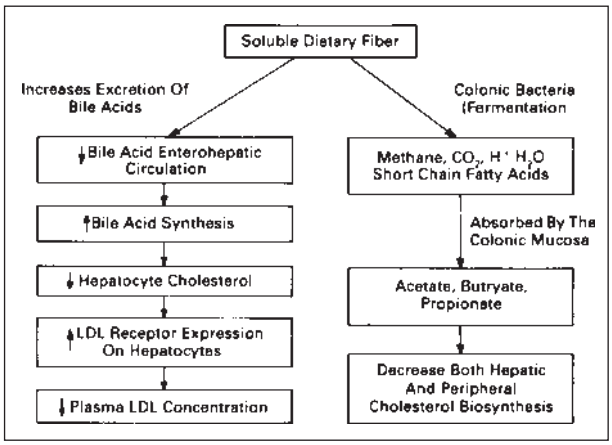

Fig. 4 - The proposed mechanism of action by which soluble dietary fiber lowers the serum cholesterol concentration

Colonic bacteria ferment soluble fiber into short-chain fatty acids, methane, carbon dioxide, hydrogen, and water[87]. A large amount of these short-chain fatty acids is absorbed by the colonic mucosa, enter the portal vein, and primarily consist of acetate, butyrate, and propionate[88]. Propionate has been shown to inhibit both hepatic and peripheral cholesterol biosynthesis and also to increase clearance of LDL from plasma[89]. Therefore, although the rate of endogenous cholesterol synthesis should be enhanced due to less dietary cholesterol being absorbed, perhaps, this stimulatory effect on HMG CoA reductase is somewhat offset by the inhibitory effect of propionate.

Potential for combination with drugs

Although dietary modification has been suggested as first-line treatment of choice for hypercholesterolemia, there are many patients in whom for various reasons, such as inherent metabolic traits, diet therapy alone is not effective. For these individuals, a variety of drugs known to decrease cholesterol levels are available, however, none of these drugs are free from adverse effects. By supplementing these various pharmacologic regimens with dietary fiber, it may be possible to reduce the drug dosage and thus decrease the risk of side effects, while concomitantly improving therapy due to the additive hypocholesterolemic effects of the two compounds.

Bile acid sequestrants, such as cholestyramine and cholestipol, have been shown to be effective in lowering serum levels of LDL cholesterol, but a common side effect is constipation. By combining a bile acid sequestrant with a soluble fiber that is known to have bulk laxative properties, such as psyllium, constipation can theoretically be avoided but cholesterol levels still lowered.

Nicotinic acid has been shown to decrease serum cholesterol by decreasing the production of VLDL, but has as an associated adverse effect the production of decreased glucose tolerance. Studies with diabetics have shown that diets rich in dietary fiber have improved glycemic control. Combinations of the two agents could potentially lower serum cholesterol, while negating this undesirable side effect. HMG CoA reductase inhibitors decrease endogenous synthesis of cholesterol. Soluble dietary fiber increases the excretion of bile acids. Both lower serum LDL cholesterol levels by increasing the number of LDL receptors on hepatocytes. Experiments have shown that combinations of a nonabsorbable agent, such as a bile acid sequestrant, with an absorbable agent, such as an HMG CoA reductase inhibitor, acted synergistically to lower serum cholesterol levels[90-92]. Therefore, it may be possible to simultaneously decrease serum cholesterol levels and increase patient safety by substituing soluble dietary fiber, a natural bile acid sequestrant, into such a regimen.

Other health benefits of dietary fiber

In addition to its cholesterol lowering effects, the inclusion of fiber in the diet has a number of other health benefits. Additional chewing involved with more abrasive fiber rich foods helps to remove plaques from teeth that play a major role in the pathogenesis of dental caries[93].

Inclusion of fiber in the diet tends to produce larger, softer fecal masses that produce less strain while passing stools, thus decreasing the risk of diverticular diseased[94,95], hiatus hernia[96,97], and varicose veins[98], all of which are associated with increased intra-abdominal pressure. Fiber-rich diets that produce softer stools and less straining have also been useful in the treatment of hemorrhoids[94,101]. Dietary fiber may reduce the production and excretion of fecal carcinogens and studies have revealed an inverse relationship between the intake of dietary fiber and the incidence of colon cancer[109-110]. Addition of fiber to the diet, especially wheat fiber, may decrease the risk of gallstones and thus secondary reduce the risk of gall blader cancer[6,111]. Adding bulk to food fiber induces society, yet, at the same time, it may help in weight managementof obese subjects by providing a greater volume of food with fewer calories[102-106]. Dietary fiber has also been shown to improve glycemic control and reduce insulin requirements in diabetic subjects. Finally, dietary fiber also lowers serum triglyceride levels[107,108] that combined with its hypocholesteremic effect protects from CHD[42,43,45] and hypertension[112,115].

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