Soluble fiber and nondigestible carbohydrate effects on plasma lipids and cardiovascular risk

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The association between elevated plasma LDL-cholesterol concentrations and increased risk for heart disease has made the scientific community aware of dietary sources that might effectively reduce plasma cholesterol levels. Several large-scale cohort studies have documented that dietary fiber lowers the risk for coronary heart disease. In addition, there is substantial evidence from randomized controlled clinical trials that a mean reduction of 9% in LDL-cholesterol can be achieved by intake of different sources of soluble fiber. Incorporating fiber sources into our diet may provide a useful adjunct to a low-saturated fat diet, and may have a further beneficial effect for individuals who have mild-to-moderate hypercholesterolemia. The physicochemical properties of soluble fiber result in important modifications in volume, bulk and viscosity in the intestinal lumen, which will alter metabolic pathways of hepatic cholesterol and lipoprotein metabolism, resulting in lowering of plasma LDL-cholesterol. Curr Opin Lipidol 12:35–40. © 2001 Lippincott Williams & Wilkins.

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Abbreviations

CETP	cholesterol-ester transfer protein
CVD	cardiovascular disease
Cyp7	cholesterol 7α-hydroxylase
NDC	nondigestible carbohydrates

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Introduction

Intake of whole grains [1••,2], cereals [3], fruits and vegetables, which are major sources of soluble fiber, has been associated with positive effects on plasma LDL-cholesterol concentrations and with decreased risk for cardiovascular disease (CVD). Consumption of these products provides the additional favorable effects of phytochemicals and antioxidants [4], and the presence in these foods of monounsaturated fatty acids [5] and n-3 polyunsaturated fatty acids [6] may add to the beneficial effects on plasma lipid profiles. Although dietary recommendations are that 25–30 g dietary fiber should be consumed each day, intake is much lower in some countries such as the USA [7]. A recent study [8], which analyzed results from 6206 individuals in order to identify constraints in adopting the recommendations for fiber intake, reported that only 15% of individuals consumed fruits and vegetables frequently.

Numerous clinical [5,9•,10] and animal studies [11–13] have demonstrated the hypocholesterolemic properties of dietary soluble fiber. Intensive research has provided substantial information on the plasma LDL-cholesterol-lowering mechanisms that underlie such properties. Major advances in mechanistic approaches which help clarify the role of soluble fiber in lowering plasma cholesterol, have been achieved by the use of animal models [11–16].

Dietary fiber: definition and classification

'Dietary soluble fiber' is an ambiguous term that mainly distinguishes the water-soluble properties of nondigestible carbohydrates (NDCs) from insoluble forms of fiber, and does not adequately address the intrinsic properties of these compounds and their metabolic significance. Recently, terminology that more than expands the distinction between soluble and insoluble fiber has been proposed. Some authors prefer the term 'NDC' for all compounds that are of a carbohydrate nature, with similar physiologic effects to those of soluble fiber [4]. 'Viscous fiber' is used by some authors [17], because it has been recognized that viscosity plays a major role in the physicochemical properties of fiber and the resulting physiologic responses [18,19].

For the present review, the term 'soluble fiber' will be used to include the effects of all NDCs on blood lipid levels and CVD risk, and the mechanisms that are attributed to the hypolipidemic effects of fiber.

Soluble fiber and cardiovascular disease risk factors: recent cohort studies

An analysis of the change in CVD risk factors over 10 years was conducted in young healthy black and white adults in a multicenter, population-based cohort study including 2909 participants [20••]. After adjusting for baseline values of body size, sex, age, education, energy intake, physical activity, cigarette smoking and vitamin supplement use, dietary fiber had a negative linear association from lowest to highest quintile with the following parameters: weight ($P < 0.001$), waist to hip ratio ($P = 0.01$) and fasting insulin ($P = 0.007$). In addition, the highest fiber intake was associated with lower blood pressure, plasma LDL-cholesterol and triglycerides, and fibrinogen levels. That study did not examine specific effects of fiber sources such as whole grain, vegetables, and fruit. Thus, the decrease in all those CVD risk factors could be attributed to the high fiber content or to biologically active constituents (antioxidants, phytochemicals) associated with fiber consumption.

Measurements of whole grain and refined grain products were obtained from the Nurses' Health Study [1••], which included 75 521 female nurse participants, in order to evaluate whether whole grain intake reduces the incidence of CVD in women. After adjusting for age, smoking, body mass index, postmenopausal hormone use, alcohol intake, multivatimin, vitamin E and aspirin use, and physical activity, an inverse relationship between whole grain intake and CVD risk was found. The relative risks were 1.0, 0.92, 0.93, 0.83, and 0.75 ($P < 0.001$) from the lowest to the highest quintiles of whole grain consumption, respectively. In the Iowa Women's Health Study [2], which included 34 492 postmenopausal women, whole grain intake and its possible relationship with CVD was evaluated. After adjustment for demographic, physiologic, and behavioral and dietary variables, relative risks were 1.0, 0.96, 0.76, 0.71, and 0.64 ($P < 0.02$) for women consuming 0.2, 0.9, 1.2, 1.9, and 3.2 servings/day, respectively. In both studies, the lower CVD risk with higher whole grain consumption was not fully explained by intake of dietary fiber or the antioxidants that are present in whole grain.

Other cohort observational studies have shown a negative association between NDC intake and CVD risk. Results from the prospective Oxford Vegetarian Study [21], which included 6000 vegetarians and 5000 nonvegetarian control individuals, indicated that fiber intake was inversely associated with total cholesterol concentrations in both men and women. The Scottish Heart Study [22••], which included 11 260 men and women, investigated the relationship between antioxidant and fiber intake on incident CVD and all-cause mortality. For both men and women, lower intakes of dietary fiber were associated with a greater number of CVD cases and non-CVD deaths ($P < 0.001$).

In a prospective cohort of postmenopausal women from the Iowa's Health Study [23], a significant negative correlation between dietary fiber and chronic disease was reported. This study included 3515 sisters who consumed the same meals, indicating that the clustering of complex diseases may in part be attributed to diet. US women from the Nurses' Health study (68 782 participants) [24••] in the lowest and the highest quintiles for dietary fiber intake were compared. Among different sources of dietary fiber, only cereal fiber was associated with a reduced risk for CVD.

These cohort studies support contention that there is an inverse association between dietary fiber intake and decreased risk for CVD. After adjusting for the most important confounding variables, including body mass index, age, smoking and vitamin supplementation, the association persisted. The beneficial effect of fiber appears to be mostly related to consumption of cereal and grain sources.

Hypocholesterolemic effects of different types of soluble fiber

Soluble fiber has been consistently shown to reduce plasma LDL-cholesterol. The types of fiber used range from the most conventional and studied sources such as pectin [9•], seeds from *Plantago ovata* (psyllium) [25•,26], β-glucan from oat bran [27•], guar gum [9•] and rye bread [28], to those that may be classified as unconventional. Among the unconventional fiber sources are included pectin derived from prickly pear [29], β-glucan from yeast [30], and fiber from the husks of lime treated corn [31•]. In addition, there are a number of components that are resistant to enzyme digestion such as resistant starch, which has similar properties to those of dietary fiber, and reduces plasma cholesterol in rats [32•] and guinea pigs [33].

The plasma LDL-cholesterol lowering that occurs with intake of psyllium has been confirmed in recent studies [10,25•,34•]. For example, psyllium proved to be an effective adjunctive therapy in hypercholesterolemic men and women [10], and reduced LDL-cholesterol by 6.7%. The safety and efficacy of psyllium in individuals with type 2 diabetes was established by showing no adverse effects in the participants and a 13% lowering of LDL-cholesterol [25•]. In contrast, konjac-mannan did not reduce LDL-cholesterol or apolipoprotein B in type 2 diabetic patients [35]. However, decreases in total cholesterol : HDL-cholesterol ratio, serum fructosamine, and systolic blood pressure were observed in comparison with the control period, indicating that konjac-mannan intake had a beneficial effect on other risk factors for CVD.

A recent meta-analysis by Brown *et al.* [9•] evaluated the hypocholesterolemic effects of pectin, psyllium, oat bran, and guar gum from 67 controlled trials, and those investigators concluded that all fibers were equally effective in reducing plasma LDL-cholesterol. What appeared to be consistent in these studies was that plasma lipid changes were specific to LDL-cholesterol. No significant changes were observed in plasma HDL-cholesterol or triglycerides concentrations. Furthermore, no specific effects related to sex were reported. Onning *et al.* [27•] tested the effect of rye bread supplementation (20% of daily energy) in 40 hypercholesterolemic individuals (18 men and 22 women). When analyzed by tertile consumption, individuals in the highest tertile had a 12% reduction in LDL-cholesterol.

A different meta-analysis of eight controlled trials was conducted by Andersson *et al.* [34•] in order to assess more precisely the hypolipidemic effects of psyllium when used as an adjunct to low-fat diets. Those authors concluded that psyllium supplementation was well tolerated and resulted in an additional 7% reduction in LDL-cholesterol in hypercholesterolemic individuals already consuming a low-fat diet.

A review of the multiple studies that utilized oat products in the treatment of hypercholesterolemia [36••] concluded that the extent of the plasma LDL-cholesterol lowering may be related to the method of oat preparation and to the concentration of β-glucan. In that review, the potential use of a more concentrated source of β-glucan, that derived from yeast, was postulated as a useful alternative to reduce calorie consumption. Free-living individuals who received a supplement of 15 g/day of β-glucan from yeast had an 8% reduction in LDL-cholesterol and HDL-cholesterol after 8 weeks [30]. After 12 weeks, however, no significant differences were observed in plasma cholesterol levels as compared with baseline. Oat milk consumption (0.5 g/100 g β-glucan) resulted in a 6% lower plasma LDL-cholesterol compared with placebo in 52 individuals participating in a randomized, controlled, double-blind study [27•].

Dietary fiber and mechanisms of action

The clinical trials cited above mainly focused on measuring plasma lipid levels after fiber supplementation and did not address specific effects on cholesterol and lipoprotein metabolism. Mechanistic approaches can be addressed using animal models, and these are reviewed below.

Hepatic cholesterol metabolism

It is widely accepted that the primary action of fiber takes place in the intestinal lumen [18]. The major mechanism could possibly be the ability of soluble fiber to increase bile acid loss [37]. In addition, fiber effects in decreasing glycemic index may also play a role in decreasing plasma lipid levels [38]. In addition, foods with high glycemic index may stimulate lipogenesis, and increase postprandial glucose and insulin responses, indicating that glycemic index may have significant implications for the risk of obesity, diabetes and CVD [39].

From a mechanistic point of view, the alterations caused by soluble fiber in bile acid homeostasis by interrupting its enterohepatic circulation [40•] and in the rate of nutrient absorption (including lipids) will alter hepatic cholesterol metabolism by effectively reducing hepatic cholesterol concentrations. The decreases in hepatic cholesterol result from a decreased delivery of cholesterol to the liver by chylomicron remnants [11] and by a decrease in the hepatic pool of free cholesterol, the substrate for bile acid synthesis [38,41••,42]. In guinea pigs, significant reductions of hepatic cholesterol due to intake of different sources of soluble fiber have been observed [11,39,43••].

Conversion of hepatic cholesterol to bile acids represents the major regulatory pathway by which the body eliminates excess cholesterol [44]. Cholesterol hydroxylation at the α position is the initial and rate-limiting step in this process. This step is catalyzed by cholesterol 7α-hydroxylase (Cyp7), which is the main regulatory enzyme in the bile acid synthesis pathway [45]. Bile drainage or administration of bile acid-sequestering resins stimulates cholesterol 7α-hydroxylation in liver. Studies in hamsters [13] have demonstrated that there is an upregulation in the activity and the messenger RNA abundance of Cyp7 after psyllium intake, indicating a role of psyllium in increasing the degradation of cholesterol to bile acids. Similarly, increases in Cyp7 activity in guinea pigs have also been observed after pectin and psyllium intake [41••,43••]. As a result of this mechanism, free cholesterol, specifically microsomal free cholesterol, is decreased [46].

The expression of the LDL receptor gene in liver is regulated by a feedback mechanism that involves hepatic cholesterol. When the demand for cholesterol increases, the liver cells express high levels of LDL receptor messenger RNA, and when cholesterol accumulates in the cell the activity and expression of the LDL receptor is suppressed [47]. Depletion of hepatic cholesterol concentrations as a result of fiber intake leads to an upregulation of LDL receptors, as demonstrated by in-vitro measurements of hepatic LDL receptor or in-vivo determinations of LDL turnover [11,12].

Another important metabolic alteration, which takes place in liver, is increased synthesis of cholesterol within the hepatocyte, as demonstrated by higher activity of 3-

hydroxy-3-methylglutaryl coenzyme A reductase [42] or measurement of sterol synthesis *in vivo* [48]. Such a compensatory increase in hepatic synthesis occurs when intestinal cholesterol absorption is impaired or when bile acid synthesis is stimulated. Under these conditions, acyl-coenzyme A cholesteryl : acyltransferase activity is downregulated, because the availability of free cholesterol for esterification is substantially reduced [33,41••].

Lipoprotein metabolism

As a result of depleted hepatic pools due to fiber intake, lipoprotein metabolism is altered. The decreases in hepatic cholesterol have been related to lower rates of hepatic apolipoprotein B secretion in hamsters [16], guinea pigs [14] and nonhuman primates [15], and to faster LDL turnover rates in rats [49] and guinea pigs [11]. In addition, resistant starch has been shown [32•] to increase plasma propionate concentrations in rats. A role of propionate in inhibiting fatty acid synthesis, and therefore in decreasing VLDL secretion, has been discussed as a mechanism by which NDCs lower plasma LDL-cholesterol [32•].

In guinea pigs the composition of both VLDL and LDL are significantly altered by dietary soluble fiber, and these compositional modifications have metabolic implications [43••]. Soluble fiber intake results in the formation of a large triglyceride-enriched, cholesteryl ester-depleted VLDL particle; these compositional changes are associated with less conversion to IDL and LDL in the delipidation cascade [50]. It has also been postulated that large VLDL are catabolized faster by the apolipoprotein B/E receptor [51].

The resulting LDL from fiber-treated guinea pigs is a particle with a smaller diameter, less core to surface components, and a higher peak density [12,43••]. In addition LDL fractional catabolic rates are faster in guinea pigs that are fed soluble fiber [11] because of upregulation of hepatic LDL receptors [12,52] and faster LDL turnover in plasma associated with a smaller, cholesterol-depleted particle [43••].

Other important modifications which take place in the intravascular compartment are a significant decrease in cholesterol-ester transfer protein (CETP) activity, which can be associated with the cholesteryl ester-depleted VLDL and LDL [43••,53]. Lower CETP activity may contribute to the hypocholesterolemic mechanisms that are attributed to soluble fiber. In agreement with animal studies, a decrease in CETP activity in 68 individuals consuming psyllium versus placebo in a randomized crossover clinical trial has been observed (Fernandez ML, unpublished data).

Conclusion

It is clear from the epidemiologic data derived from most cohort studies that dietary fiber is associated with a protective effect against CVD. However, two major large-scale studies reported an association between whole-grain consumption and reduced risk for CVD that apparently was independent of dietary fiber [1••,2]. Results from two recently published meta-analyses [9•,34•], along with data from clinical studies, reported in the past two years [6,25•,27•] support the cholesterol-lowering properties of psyllium, pectin and guar gum. A consistent finding in these studies [6,9•,25•,27•,34•] was significant reductions in LDL-cholesterol in the order of 6–15%, and no changes in HDL-cholesterol or triglycerides. These clinical studies emphasize the importance of including the recommended amounts of soluble fiber in the diet because of its beneficial effect in lowering plasma cholesterol and its protective effect against CVD.

Most of the human studies have not addressed specific mechanistic effects of fiber on cholesterol and lipoprotein metabolism. From the animal studies, important data have emerged to demonstrate how the physicochemical properties of fiber and NDCs in the intestinal lumen have a very significant repercussion on hepatic cholesterol metabolism and on the synthesis, processing in the intravascular compartment and catabolism of lipoproteins. The main outcome of fiber action is a lowering of hepatic cholesterol pools as a result of cholesterol being diverted to bile acid synthesis and less cholesterol delivery to the liver through chylomicron remnants. The major regulatory enzymes of cholesterol homeostasis are then modified. 3-Hydroxy-3-methylglutaryl coenzyme A reductase activity and Cyp7 are upregulated, the former to compensate for sterol loss in liver and the latter to produce more bile acids to balance the depletion of bile acid pools. In addition, acyl-coenzyme A cholesteryl : acyltransferase activity is decreased because of less availability of substrate (free cholesterol). Furthermore, hepatic LDL receptors are upregulated to re-establish a cholesterol balance in liver and contribute to the lowering of LDL-cholesterol by removing LDL from plasma. In addition, VLDL apolipoprotein B synthesis rate is decreased, the conversion of VLDL to LDL is reduced, and CETP activity is lowered. The combination of all of these mechanisms results in the consistent hypocholesterolemic effect induced by soluble fiber.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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