Nutritional and Health Benefits of Inulin and Oligofructose

Impact of Nondigestible Carbohydrates on Serum Lipoproteins and Risk for Cardiovascular Disease[1]

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ABSTRACT Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death in the U.S. and in most developed countries. Many nutritional factors contribute to risk for ASCVD including total and saturated fat consumption, fruits and vegetables in the diet and dietary fiber intake. This review will focus on the relationship of dietary fiber intake to risk for coronary heart disease (CHD) and ASCVD (which includes, principally, CHD, cerebral vascular disease and peripheral vascular disease). Fiber-rich foods such as vegetables, fruits, whole-grain cereals and legumes are rich sources of nutrients, phytochemicals and antioxidants. For example, most high fiber foods contain soluble and insoluble fiber, minerals, vitamins, other micronutrients and phytochemicals. Cereals and legumes also contain complex carbohydrates and unsaturated fatty acids. Some high fiber foods are rich in monounsaturated fatty acids, whereas others provide (n-3) fatty acids. Legumes and certain vegetables provide oligosaccharides. When assessing the health benefits of dietary fiber, one should consider the potential effects of associated nutrients, micronutrients and phytochemicals. These interactions will be reviewed as we discuss relationships of dietary fiber to ASCVD. J. Nutr. 129: 1457S–1466S, 1999.

KEY WORDS: •

DIETARY FIBER AND CORONARY HEART DISEASE

The evidence for links between dietary fiber and atherosclerotic cardiovascular disease (ASCVD)[3] is very strong;it arises from animal studies (Pilch 1987), epidemiologic observations (Rimm et al. 1996) and a limited number of clinical trials (Anderson 1995a). In addition, there is a strong theoretical rationale for this link, making the association a logical one. Trowell (1972) proposed that a deficient fiber intake might contribute to the high prevalence of coronary heart disease (CHD) among Western people and that a generous fiber intake in other areas of the world was protective from CHD. This hypothesis has gained widespread acceptance, but the scientific data in its support have been limited. Recently, Rimm et al. (1996) reported that higher levels of fiber intake were associated with lower rates of myocardial infarctions and death from CHD among U.S. male health professionals. This prospective cohort study probably provides the most persuasive support for the Trowell hypothesis linking dietary fiber intake to protection from coronary heart disease.

Since the report of Morris et al. (1977), epidemiologists have reported a strong link between dietary fiber intake and prevalence of CHD (Rimm et al. 1996). Vegetarian populations have higher fiber intakes than nonvegetarian control populations (Beilin 1994, Kritchevsky et al. 1984) and experience better health and fewer premature deaths (Anderson 1990). All-cause mortality is significantly lower for vegetarian than for age- and gender-matched nonvegetarian individuals (Kahn et al. 1984, Lemon and Walden 1966); this reduction is related, in part, to a significant reduction in CHD mortality (Kristein et al. 1977, Ruys and Hickie 1976, Wynder 1959). Although the health benefits associated with vegetarian diets can be attributed, in part, to physical activity and other healthy lifestyle practices, the increased dietary fiber intake appears to make a significant contribution (Anderson 1990, Rimm et al. 1996).

Over the past 20 years, numerous studies have examined the association between dietary fiber intake and risk for CHD. Rather remarkably, all of these studies suggest that there is a negative relationship when evaluating dietary fiber intake with CHD. Seven studies (Burr and Sweetman 1982, Hallfrisch et al. 1988, Khaw and Barrett-Connor 1987, Kromhout et al. 1982, Kushi et al. 1985, Liu et al. 1982, Morris et al. 1977) noted the negative association specifically with dietary fiber; the remainder used other markers of fiber intake such as legume intake, salad intake, complex carbohydrate or vegetable protein intake.

Research findings may depend on the epidemiologic design,

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[3] Abbreviations used: AHA, American Heart Association; apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CA, cholic acid; CDCA, chenodeoxycholic acid; CHD, coronary heart disease; DCA, deoxycholic acid; HCFC, high carbohydrate, high fiber; HMG, β-hydroxyl-β-methyl glutarate; IDDM, insulin-dependent diabetes mellitus; LCLF, low carbohydrate, low fiber; LFHF, low fat, high fiber; NIDDM, noninsulin-dependent diabetes mellitus; PHGG, partially hydrolyzed guar gum.

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which can be ecological, cohort, case-comparison or population-based. Ecological studies are designed to assess the association between two variables, comparing groups whose selection is based on a variable that is not being studied, such as geographical location. Liu et al. (1982) conducted a univariate analysis on data for both men and women ages 35–74 y from 20 economically advanced countries, collecting data for the years 1965–1969. They found that fiber intake, estimated from consumption of vegetables, fruits, grains and legumes, yielded a significant inverse correlation with CHD mortality rates.

Cohort studies evaluate the association between a risk factor and the incidence of a disease as compared among two or more groups. These groups are determined on the basis of levels of exposure to a particular variable. Morris et al. (1977) published one of the first cohort studies on the health implications of a high fiber diet in cardiovascular disease. From 1956 to 1966, 7-d dietary surveys were collected from 337 middle-aged men in London and Southeast England. These men were reevaluated in 1976 to determine those who had developed clinical coronary heart disease. From this information, it was noted that dietary fiber from cereals was independently associated with a lower rate of disease. In 1973, Burr and Sweetnam (1982) recruited 10,943 subjects to test the hypothesis that risk of death from disease can be reduced by a high intake of fiber. After 7 y, no significant associations were found with fiber. However, a lower mortality from cerebrovascular disease was noted in subjects who regularly consumed whole-meal bread. A 1960 study by Kromhout (1982) enlisted the help of 871 middle-aged men in the Netherlands to evaluate risk indicators for CHD. After 10 y of follow-up, it was suggested that a diet of at least 37 g of dietary fiber per day may be protective against chronic diseases such as CHD.

Case-comparison studies assess the association between a disease state and risk factors, comparing diseased vs. nondiseased subjects. The risk factor data are often collected either concurrently or retrospectively. Khaw and Barrett-Connor (1987) evaluated the relationship between dietary fiber intake and 12-y mortality rates from ischemic heart disease in a population-based cohort of 859 men and women living in Southern California. They calculated that every 6 g increase in daily fiber consumption was associated with a 25% reduction in ischemic heart disease mortality. Kushi and collaborators (Kushi et al. 1985) examined the relation between diet and mortality from CHD in a prospective epidemiologic study of 1001 middle-aged men. Intakes of fiber, vegetable protein and starch were lower in those individuals who died from coronary heart disease. However, these observations were not significant after adjustment for other risk factors. In 1992, Bolton-Smith et al. (1992) published results of a case-comparison study in which 10,359 men and women ages 40–59 who were patients of 260 general practitioners throughout Scotland were evaluated. Subjects were divided into the categories of CHD-diagnosed, CHD-undiagnosed and non-CHD. Food-frequency questionnaires were used to record dietary habits. The results suggested that a high dietary fiber intake may be cardioprotective in both males and females.

Population surveys assess the cross-sectional association between two variables by comparing population groups. For example, one can measure the prevalence, mean value or distribution of a particular characteristic or disease in a population. Hallfrisch et al. (1988) used 7-d diet records to estimate fiber intake for the 845 men participating in the Baltimore Mean Longitudinal Study of Aging. On the basis of this information, the researchers determined that a higher fiber consumption was associated with lower levels of risk factors for coronary artery disease, including systolic and diastolic blood pressure, triglycerides and fasting plasma glucose. Recently, He et al. (1995) studied 850 Chinese subjects to evaluate the relationship of oats and buckwheat to cardiovascular disease. Dietary intake of oats and buckwheat was determined via a dietary questionnaire. Although oat intake was associated with a lower body mass index (BMI), systolic and diastolic blood pressure and HDL cholesterol, buckwheat intake was associated with lower serum cholesterol, LDL cholesterol and a higher ratio of HDL to total cholesterol.

Although several clinical trials have established an inverse relation between fiber intake and CHD, two studies (Neal and Balm 1990, Rimm et al. 1996) suggest that the intake of *cereal* fiber has the strongest negative association with CHD. This is somewhat surprising because cereal fiber, in most regions of the world reported in these studies, comes largely from wheat intake. Wheat bran does not decrease serum cholesterol and LDL cholesterol concentrations as effectively as does oat bran or psyllium, sources of soluble fiber. Perhaps the phytochemicals specific to wheat bran (Slavin 1994) may have triglyceride-lowering effects and CHD protective effects by mechanisms not related to LDL cholesterol reductions. The triglyceride-lowering effects of wheat bran are discussed in the next section.

Despite the fact that some unknowns exist about the precise mechanism mediating lipoprotein changes, substantial evidence supports the role of fiber. Ecological, cohort, case-comparison, population-based and most recently clinical trials support the inverse relationship between dietary fiber in the diet and ASCVD.

LIPOPROTEIN EFFECTS OF DIETARY FIBER

Serum cholesterol concentrations are surrogate markers for risk for CHD because LDL have a central role in the pathogenesis of atherosclerosis (Navab et al. 1996). Oxidation of LDL in the subendothelial space of arteries sets the stage for macrophage uptake of LDL, foam cell development, and ultimately fatty streak and atheroma formation (Navab et al. 1996). Decreasing the LDL cholesterol concentrations is one of the most effective means of decreasing risk for coronary heart disease (Manson et al. 1992). Dietary fiber, especially soluble, viscous fibers effectively decrease serum cholesterol and LDL cholesterol concentrations, which may contribute to their protective role against CHD (Anderson et al. 1990).

In addition to its favorable effects on fasting and postprandial serum lipoproteins, as detailed below, dietary fiber intake affects a number of other CHD risk factors. The effects of fiber intake on these factors such as hypertension, diabetes and obesity are summarized below.

Most soluble or viscous fibers have hypocholesterolemic effects (Anderson et al. 1990, Glore et al. 1994). In general, these soluble fibers, such as psyllium, oat bran, guar and pectin, decrease serum cholesterol and LDL cholesterol concentrations without affecting serum triglycerides. Often, consumption of these soluble fibers is accompanied by distinct reductions in serum HDL cholesterol concentrations. For example, in studies of the effects of dry beans on serum lipoprotein concentrations, we noted that consumption of 100 g of dry beans per day, without other changes in macronutrient consumption, was accompanied by a 16.1% net reduction (bean change minus control change) in serum LDL cholesterol concentrations and a 9.9% net reduction in serum HDL cholesterol concentrations (Anderson 1995b).

Animal models provide a suitable approach for comparing lipid-lowering effects of dietary fibers under controlled conditions. We have performed >30 such studies comparing 6–10

TABLE 1

Response of serum and liver cholesterol and serum triglyceride concentrations to intake of different dietary fibers in a rat model[1]

Fiber	Number of studies	Serum cholesterol *% change*	Liver cholesterol *% change*	Serum triglycerides	
				mg/dL	*% change*
Psyllium	7	−32 ± 6	−52 ± 5	169 ± 15	−9.6
Oat gum	11	−22 ± 3	−45 ± 7	169 ± 11	−9.6
Guar gum	3	−23	−43	NA	NA
Pectin	20	−17 ± 4	−35 ± 6	193 ± 12	+3.2
Oat bran	8	−12 ± 2	−28 ± 6	162 ± 14	−13.4
Soy fiber	6	−11 ± 2	−17 ± 3	168 ± 15	−10.2
Corn bran	2	−6	−11	105	−43.9
Cellulose	26	0	0	187 ± 13	0.0
Wheat bran	5	−1 ± 11	+6 ± 1	116 ± 12	−38.0

[1] Values are means ± SEM; NA, not available. Cholesterol values are expressed as percentage change from cellulose values in the same experiment. Serum triglycerides are mean values from the indicated number of studies. Modified from Anderson (1995a).

fibers in each study with ~10 rats in each treatment (Anderson et al. 1994, Anderson 1995a). **Table 1** provides information about the effects of different fibers on serum lipids of rats after 3 wk of consuming purified diets providing ~67% carbohydrate, 15% protein, 6% fat, 6% dietary fiber, 1% cholesterol, 0.2% cholic acid, vitamins and minerals (Anderson 1995a). In this model, psyllium had the largest cholesterol-lowering effect by decreasing serum cholesterol by 32% and liver cholesterol by 52%. Oat gum and guar gum were slightly less effective and decreased serum cholesterol by ~22%, compared with values for cellulose-fed rats. Pectin has been reported to have a wide range of effects, depending on molecular weight and degree of methoxylation (Ebihara et al. 1979, Jud and Truswell 1982), whereas oat bran and soy fiber produce modest effects (Anderson et al. 1994, Anderson 1995a).

The serum triglyceride responses to these diets are of interest and have not been discussed previously. In a pioneer study in 1974, Heaton and Pomare (1979) reported that wheat bran intake decreased serum triglyceride concentrations in humans. Because wheat bran does not have a significant effect on serum cholesterol concentrations, these observations have not been carefully pursued. From our rat studies, it is clear that soluble fibers such as psyllium, oat gum and pectin do not have significant effects on serum triglycerides. However, wheat bran was associated with a major triglyceride-lowering effect; corn bran, with a limited number of observations, also appears to lower serum triglycerides.

In humans, psyllium and guar gum appear to be the most effective cholesterol-lowering soluble fibers (Anderson et al. 1990). The hypocholesterolemic effects of psyllium (Olson et al. 1997), guar gum (Todd et al. 1990) and oat bran (Ripsin et al. 1992) are well documented by meta-analyses. Our 1990 analysis of 23 human studies described the effects of guar gum supplementation on serum cholesterol. A median reduction of 11% (range, from +3% to −38%) was noted with inclusion of guar gum in the diet. Significant reductions in serum cholesterol levels were found in 20 of the 23 studies evaluating guar gum supplementation (Anderson et al. 1990). Similarly, a 1992 meta-analysis by Ripsin et al. (1992) tested the hypothesis that oat supplementation would lower serum cholesterol levels. Ten clinical trials were evaluated, and a reduction of 5.9 mg/dL (−0.13 mmol/L) in total cholesterol was noted in subjects consuming an oat supplement. However, the most significant reductions were found in trials that used hypercholesterolemic subjects with initially higher cholesterol levels.

Pectin also has significant hypocholesterolemic effects (Anderson et al. 1990), whereas soy fiber has a modest effect in humans (Lo et al. 1986). A summary of 19 clinical studies evaluating the effects of pectin supplementation on serum cholesterol was included in our 1990 analysis. A median reduction of 8% (range, −5 to −18%) in total cholesterol was noted in subjects receiving pectin in their diet. A significant reduction in total cholesterol was found in 13 of the 19 trials evaluated (Anderson et al. 1990). Other less widely studied and used soluble fibers, such as locust bean gum (Zavarol et al. 1983) and konjac mannan (Anderson et al. 1990), have modest hypocholesterolemic effects.

The effects of soluble fiber intake on specific lipoproteins is of great importance. LDL cholesterol appears to be the most atherogenic lipoprotein (Navab et al. 1996), but HDL cholesterol has an extremely important counterbalancing effect (Gowri 1997). The atherogenicity of triglyceride-rich particles is still debated, but postprandial hypertriglyceridemia probably contributes to risk for CHD (Anderson et al. 1995b). Because LDL particles carry ~65% of the cholesterol in serum, changes in total serum cholesterol values largely follow changes in serum LDL cholesterol concentrations. Soluble or viscous fibers have specific effects on LDL cholesterol and exert only minimal effects on other lipoprotein particles. In our meta-analysis of eight studies conducted in a comparable manner, administration of 10.4 g of psyllium daily for 8 wk to hypercholesterolemic subjects consuming an American Heart Association (AHA) Step I diet was accompanied by a net reduction (psyllium minus placebo) of 6.7% in LDL cholesterol ($P < 0.0001$) (Anderson, J. W., unpublished observations). Similarly, specific effects on LDL cholesterol concentrations have also been noted in subjects consuming oat bran (Ripsin et al. 1992).

Although psyllium and oat bran tend to decrease HDL cholesterol concentrations slightly, these changes are not significant. Because HDL cholesterol is an umbrella term for a variety of small lipoprotein particles, namely, HDL_2, HDL_3, as well as apolipoprotein (apo) A-I (only) and apo A-I/A-II particles (Silverman and Pasternak 1993), measurements of the total HDL cholesterol concentration have serious limitations. Recent studies indicate that specific interventions affect the antiatherogenic HDL particles (HDL_2 and apo A-I particles) selectively, whereas other interventions tend to affect the neutral or atherogenic HDL particles (apo A-I/A-II) (Silverman and Pasternak 1993). Estrogens may increase concentrations of antiatherogenic HDL particles, whereas alcohol may increase the less protective particles (Silverman and Pasternak

1993). The effects of dietary fibers on the specific HDL subfractions are not well delineated. In our meta-analysis (Anderson, J. W., unpublished observations), we noted that psyllium supplementation slightly increased the serum apo-A-I concentrations and significantly increasing the apo-A-I/apo-B ratio. Further studies are required to understand the specific effects of soluble fibers on HDL subfractions.

MECHANISMS FOR HYPOCHOLESTEROLEMIC EFFECTS

The cholesterol-lowering effects of soluble or viscous fibers relate to their gel-forming properties (Anderson 1995b). Soluble fibers, such as gum acacia, which do not form viscous solutions in water, appear to have minimal hypocholesterolemic effects (Haskell et al. 1992).Similarly, hydrolyzed guar gum does not have significant cholesterol-lowering benefits in humans (Anderson et al. 1993).

Soluble fibers such as psyllium and oat bran appear to exert their principal effects on cholesterol metabolism through decreases in bile acid absorption. These soluble fibers bind bile acids in the small intestine, alter micelle formation and decrease their absorption in the small intestine. Consequently, more bile acids are excreted with the feces. Oat bran, for example, increases fecal bile acid loss more than twofold and increases loss of deoxycholic acid (DCA) by 240% (Marlett et al. 1994). Psyllium also increases bile acid excretion significantly and selectively increases the fractional turnover of both chenodeoxycholic acid (CDCA) and cholic acid (CA) (Everson et al. 1992). Acting somewhat like bile-acid binding resins, these soluble fibers deplete the bile salt pool and divert cholesterol synthesis from lipoprotein precursors to bile acid synthesis. Short-chain fatty acid (SCFA) effects on the liver may hamper the ability of the liver to compensate for these changes in cholesterol synthetic needs (Wright et al. 1990).

Martlett et al. (1994) evaluated nine normolipidemic young men fed a control diet with or without oat bran for 2 mo. Serum CA and CDCA were measured using radiolabeled carbon as a means to monitor bile acid kinetics. Results of this study indicated that bile acid excretion and concomitant increases in bile acid synthesis are primary contributors to changes in cholesterol absorption. They found that, when subjects consumed the oat bran diet, total daily fecal bile acid excretion more than doubled, with a significant elevation in secondary bile acid excretion as well. Although the total bile acid pool was unchanged, the CA pool size decreased, whereas the DCA pool doubled. This elevation in DCA is significant because DCA inhibits primary bile acid synthesis by affecting hepatic cholesterol 7 α-hydroxylase activity and by inhibiting β-hydroxyl-β-methyl glutarate (HMG)-CoA reductase activity, the rate-limiting step in cholesterol synthesis (Marlett et al. 1994). In addition, DCA serves as a more effective inhibitor of cholesterol absorption than chenodeoxycholic acid (CDCA) in healthy humans (Leiss et al. 1984).

SCFA production in the colon, absorption into the portal vein and effects on the liver appear to play a minor regulatory role in attenuating hepatic cholesterol synthesis (Anderson 1995c, Anderson and Chen 1979, Wright et al. 1990). After meals containing soluble fibers, serum acetate levels increase, reflecting more delivery of SCFA to the liver. Our in vitro data suggest that propionate specifically inhibits cholesterol and fatty acid synthesis in the liver (Wright et al. 1990). It seems likely that the combination of bile acid loss and mild attenuation of hepatic cholesterol synthesis results in lower serum cholesterol and LDL cholesterol concentrations. Although it could be tested,, this hypothesis has not been examined carefully in humans.

Although fiber-rich foods are associated with significant protection from CHD and viscous hydrolyzed fibers have hypocholesterolemic effects, these effects may be minimized if purified fibers are used. For example, guar gum has significant cholesterol-lowering effects (Anderson et al. 1990), whereas hydrolyzed guar gum lacks this effect (Anderson et al. 1993). Furthermore, although soy proteins rich in soy isoflavones have significant hypocholesterolemic effects (Anderson et al. 1995a, Anthony et al. 1996, Wagner et al. 1997), purified isoflavone supplements may lack this effect (Nestel et al. 1997). Thus, hydrolysis of fibers and isoflavones to extract them for use as supplements may alter their physiologic effectiveness.

DIETARY FIBER EFFECTS ON NON-LIPOPROTEIN CHD RISK FACTORS

Hypertension. Controlled clinical trials have failed to provide persuasive evidence that increased fiber intake is associated with a decrease in blood pressure. However, epidemiologic studies support the hypothesis that higher levels of dietary fiber intake are associated with lower levels of systolic as well as diastolic blood pressure (Ascherio et al. 1992, Joffres et al. 1987, Witteman et al. 1989). In addition, research with vegetarian subjects, who have higher intakes of dietary fiber than control subjects, has found that the vegetarians have lower blood pressures than their matched controls (Sacks et al. 1975). Median reductions of 3.5 mm Hg in systolic and 2.2 mm Hg in diastolic blood pressure were noted in three controlled studies using vegetarian diets (Wright et al. 1979). Similarly, Appel et al. (1997) reported that a diet that is rich in fruits, vegetables and low fat dairy foods can substantially lower blood pressure. The DASH Collaborative Research Group enrolled 459 adult subjects with systolic blood pressures $<$160 mm Hg and diastolic blood pressures between 80 and 95 mm Hg. After 3 wk of consuming a control diet, subjects were randomly allocated to a diet rich in fruits and vegetables, a combination diet rich in fruits, vegetables and low fat dairy foods, or a control diet for 8 wk. At the end of treatment, systolic and diastolic blood pressure had dropped 5.5 and 3.0 mm Hg more, respectively, with consumption of the combination diet and were 2.8 and 1.1 mm Hg higher, respectively, with the fruit and vegetable diet compared with the control diet. This reduction in blood pressure was most significant in subjects with an initial systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg or both.

Unfortunately, a vast array of clinical trials has produced conflicting results, making it difficult to form concrete recommendations concerning use of dietary fiber as a means to lower blood pressure. Although it appears that a negative correlation exists, further research is required to understand the variation in blood pressure response seen across human trials.

Obesity. Obesity has been found to be an independent risk factor for coronary heart disease (Manson et al. 1995, Solomon and Manson 1997). Research supports the role that dietary fiber plays in controlling obesity by offering a prolonged feeling of satiety. A study of 50 male college students was designed to determine the effects of a high fiber diet on subsequent food intake. It was determined that adding 5.2 g of crude fiber to a meal significantly reduced food intake. In addition, those subjects receiving the high fiber meal felt significantly fuller than did the lower fiber subjects immediately after eating (Porikos and Hagamen 1986). A similar controlled study by Rigaud et al. (1987) enlisted the help of 20

healthy young volunteers who received either a high fiber supplement (7.3 g fiber per day) or placebo (0.6 g fiber per day). Visual analog scales were used to evaluate feelings of hunger immediately after each of three main meals. Mean hunger ratings were significantly greater during the control period compared with during fiber treatment. Rytigg et al. (1989) conducted a 52-wk controlled study to determine the effects of a dietary fiber supplement on weight maintenance and reduction in 90 female subjects with uncomplicated excess weight of 110–130% of ideal body weight. It was noted that hunger feeling in the fiber group decreased significantly at all three meals compared with placebo.

These three studies offer support to the suggestion that a diet rich in fiber can help control appetite by increasing satiety. With the new United States health standards, which indicate that a BMI $>$ 25 increases CHD risk (NHLBI Communications 1998), it is prudent to reduce weight, especially in the Western world where waistlines continue to expand.

Diabetes and hyperinsulinemia. An estimated 70–80 million persons in the United States have insulin resistance. Insulin resistance is an important risk factor in the development and progression of hypertension, dyslipidemia, obesity, diabetes (Ferrannini et al. 1987, Lillioja et al. 1993, Reaven 1988) and possibly CHD (Pyorala 1997, Stout 1990). A diet rich in fiber has been shown to improve insulin sensitivity (Anderson et al. 1991, Fukagawa et al. 1990) and lower serum insulin concentrations (Wolever and Jenkins 1986).

A controlled, random allocation, crossover, metabolic study (Anderson et al. 1991) allocated 10 subjects with insulin-dependent diabetes mellitus (IDDM) to a low carbohydrate, low fiber (LCLF) or a high carbohydrate, high fiber (HCHF) diet for 28 d at a time. The HCHF diet provided 35 g dietary fiber/1000 kcal in the form of whole-grain or bran cereals, dried beans, vegetables and fruit. Compared with the LCLF diet, the HCHF diet reduced basal insulin requirements and increased carbohydrate disposed of per unit insulin. This study indicated that Type 1 diabetic subjects were more sensitive to insulin when consuming a high carbohydrate, high fiber diet than when consuming a low carbohydrate, low fiber, high fat diet. High carbohydrate, high fiber, low fat diets have also been recommended for patients with Type 2 diabetes. A diet of 63–65% of energy from carbohydrates, 10–12% of energy from fat and 45 g/d of fiber for 2 wk was found to offer a significant benefit in metabolic control in volunteers with noninsulin-dependent diabetes mellitus (NIDDM). A similar improvement was not seen in a complementary high carbohydrate, low fat diet that was low in fiber (20 g/d) (O'Dea et al. 1989).

Fukagawa et al. (1990) studied 12 healthy individuals to examine the effects of a HCHF diet. The HCHF diet provided 68% of energy as carbohydrates and 33 g/1000 kcal of dietary fiber compared with 43% of energy as carbohydrates and 7g/1000 kcal of dietary fiber for the control diet. The HCHF diet was followed for 21–28 d. The HCHF diet lowered fasting serum glucose levels from 5.3 $\pm$ 0.2 to 5.1 $\pm$ 0.1 mmol/L ($P < 0.01$) and insulin from 66.0 $\pm$ 7.9 to 49.5 $\pm$ 5.7 pmol/L ($P < 0.01$). In addition, glucose disposal rates increased from 18.87 $\pm$ 1.66 μmol/(kg·min) in those consuming the control diet compared with 23.87 $\pm$ 2.78 μmol/(kg·min) ($P < 0.02$) for those provided the HCHF diet. From these results, the authors concluded that a HCHF diet may improve carbohydrate metabolism by enhancing peripheral sensitivity to insulin in healthy adults.

Results of these controlled research trials have been supported by a cohort study of 65,713 women, ages 40–65 y, involved in the Longitudinal Nurse's Health study. Participants completed a dietary questionnaire in 1986 at which time subjects were free from diagnosis of cardiovascular disease, cancer or diabetes. After 6 y of follow-up, 915 cases of NIDDM had been documented. It was determined that cereal fiber intake was inversely associated with risk of diabetes when comparing extreme quintiles. From this observation, the authors suggested that grains should be consumed in a minimally refined form to reduce the incidence of diabetes (Salmeron et al. 1997b). Similar results for disease risk were also seen in adult males (Salmeron et al. 1997a). Thus, dietary fiber intake appears to decrease the risk for developing Type 2 diabetes.

Clotting factors. Although difficult to delineate from other dietary factors in a high fiber diet, it appears that dietary fiber intake may affect blood coagulation factors. Marchmann and collaborators (Marchmann et al. 1994) conducted a dietary intervention study of healthy middle-aged Danish men and women during which they received either a traditional high fat diet or a diet that was low fat, and high fiber (LFHF). The LFHF diet significantly decreased plasma factor VII coagulant activity and increased plasma fibrinolytic activity. This reduction in plasma factor VII may be physiologically important because an 8% reduction in factor VIIc might reduce the risk for CHD by 15–20% over 5 y.

NON-FIBER PLANT COMPOUNDS AND CHD RISK

Vegetables, fruits, grains and legumes are important dietary sources of phytochemicals, antioxidant vitamins and certain (n-3) fatty acids. The potential role of these compounds is reviewed briefly below; limited information exists on the specific effects of α-linolenic acid, a plant (n-3) precursor of longer-chain (n-3) "fish oils," and this subject has been reviewed elsewhere (de Lorgeril et al. 1994, Harris 1997).

Phytochemicals. Phytochemicals are biologically active plant compounds that are "semi-essential" but are not classified currently as vitamins or minerals (Kuhnau 1976). Howard and Kritchevsky (1997) reviewed the knowledge relating CHD risk to three classes of phytochemicals, i.e., plant sterols, flavonoids and plant sulfur compounds. Each will be briefly reviewed below for their potential role with respect to risk for CHD.

Plant foods contain a number of sterols that differ from cholesterol by small differences in their side chains. The most prominent ones are sitosterol, stigmasterol and campesterol; the total amount of plant sterols in the Western diet approaches the amount of dietary cholesterol (Howard and Kritchevsky 1997). These plant sterols are poorly absorbed and appear to decrease cholesterol absorption (Mattson et al. 1982). By this mechanism, plant sterol intake may decrease serum cholesterol concentrations by as much as 10%. A recent clinical study of hypercholesterolemic individuals suggests that the daily intake of 1.9–2.6 g of sitosterol in a margarine preparation over a 1-y period was associated with a 10.2% reduction in serum cholesterol concentrations (Miettinen et al. 1995). From the amounts of plant sterols required to significantly decrease serum cholesterol concentrations, it seems unlikely that the amounts of these sterols consumed by average individuals would affect serum cholesterol concentrations (Denke et al. 1994).

The plant flavonoids are a variety of chemical compounds that are derivatives of 2-phenyl-1-benzopyran-4-one; they occur naturally in vegetables, fruits, tea and wine (Hertog et al. 1993, Howard and Kritchevsky 1997). Major sources of flavonoids in the diet are tea, red wine, onions and apples (Hertog et al. 1993). Several epidemiologic studies indicate

that higher flavonoid intakes are associated with lower rates of CHD (Hertog et al. 1993 and 1995, Knekt et al. 1996). These flavonoids appear to decrease risk for CHD by several different mechanisms. Soy proteins, rich in isoflavones, have significant hypocholesterolemic effects (Anderson et al. 1995d). Intakes of soy protein (Anderson et al. 1995d) or green tea (Simons et al. 1995), probably acting through their flavonoids, have a tendency to increase serum HDL cholesterol concentrations. Catechins, soy isoflavones and phenolic substances from red wine have important antioxidant properties and apparently are transported by LDL so that they protect against in vitro oxidation of LDL (Anderson et al. 1998, Frankel et al. 1993, Simons et al. 1995). Soy isoflavones and other flavonoids also appear to decrease platelet aggregation (Wilcox and Blumenthal 1995) and blood clotting, thereby decreasing the tendency to thrombosis (Gryglewski et al. 1987). Although soy isoflavones are not well quantified in humans (Nestel et al. 1997), studies in monkeys (Honore et al. 1997) suggest that they exert favorable effects on blood vessel dilatation similar to the effects of estrogens; thus, flavonoids may decrease risk of CHD through protective effects on blood vessels.

Sulfur-containing plant foods such as garlic also have hypocholesterolemic effects and decrease the tendency to form arterial thromboses. The allium family of vegetables, which includes onions, garlic and leeks, provides a variety of sulfur compounds that have been used for medicinal purposes for millennia (Howard and Kritchevsky 1997). Although two recent meta-analyses (Silagy and Neil 1994, Warshsky et al. 1993) report significant hypocholesterolemic effects of garlic intake, a recent well-controlled clinical trial (Simons et al. 1995) failed to detect a significant effect. Further clinical studies are required to demonstrate more clearly the effect of garlic or garlic powder intake on serum lipoproteins, platelet aggregation, coagulation time and blood pressure (Howard and Kritchevsky 1997).

Antioxidants. The LDL-oxidation hypothesis for atherosclerosis, as outlined above, supports the potential protective role of antioxidant-rich foods and supplements. Briefly, considerable experimental and clinical data suggest that oxidative modification of LDL contributes to the initiation of the plaque formation in the subendothelial space of blood vessels (Navab et al. 1996). Vitamin E, the major antioxidant transported in the LDL particle, has the potential to reduce oxidative modification of LDL through its potent chain-breaking antioxidant action (Dieber-Rotheneder et al. 1992). Indeed, early epidemiologic and observational studies (Gey 1991, Kardinaal et al 1993, Regnstom et al. 1996, Riemersma et al. 1991) support the hypothesis that a generous intake of vitamin E is associated with a reduced risk for CHD. Three large epidemiologic cohort studies (Knekt et al. 1996, Rimm et al. 1993, Stampfer et al. 1993) all reported significant reductions in risk for CHD events with reductions ranging from 31 to 65% (Jha et al. 1995). The recent report of Kushi et al. (1996) noted that CHD risk is 62% lower in women with the greatest vitamin E intake. Many clinical studies (Abbey et al. 1993, Dieber-Rotheneder et al. 1992, Fuller et al. 1996, Jialal et al. 1995, Princen et al. 1992, Reaven et al. 1995) document the association of vitamin E supplementation with a significant reduction in the in vitro oxidation of LDL. As Jha et al. (1995) summarized, the earlier prospective clinical trials did not report significant benefits for vitamin E supplementation. The Cambridge Heart Antioxidant Study (CHAOS) (Stephens et al. 1996) was a double-blind placebo-controlled study that randomized 2002 patients with angiographically proven CHD. Half of the patients received either 400 or 800 IU vitamin E; the remainder received placebo. Vitamin E intake was associated with a significant 47% reduction in CHD events (Stephens et al. 1996). Because of the conflicting results of these earlier trials, definitive conclusions must be delayed until additional trials are completed (Prince et al. 1991).

β-Carotene is also an antioxidant vitamin that is transported in LDL and has a potential to decrease LDL oxidation (Esterbauer et al. 1991). Epidemiologic studies suggest that there is an inverse relationship between β-carotene intake and CHD risk (Gey et al. 1993, Jha et al. 1995, Kardinaal et al. 1993, Morris et al. 1977). Although β-carotene supplementation does not significantly alter in vitro oxidation of LDL (Gaziano et al. 1995, Princen et al. 1992), several clinical trials have examined the effects of β-carotene on risk for CHD. Three major randomized trials (Hennekens et al. 1996, Omenn et al. 1996, The Alpha-Tocopherol BC 1994) reported no significant alterations in CHD mortality associated with β-carotene supplementation. Because of the concerns about increased risk for lung cancer among smokers receiving β-carotene (Omenn et al. 1996, The Alpha-Tocopherol BC 1994), enthusiasm for this supplement has waned (Hennekens et al. 1996).

Vitamin C is also a potent antioxidant vitamin that is water soluble. Although not transported in the LDL particle, vitamin C protects LDL from in vitro oxidation (Frei 1991, Jialal et al. 1990). Vitamin C has the capacity to preserve vitamin E in the plasma and also repair oxidative damage inflicted on vitamin E (Esterbauer and Ramos 1995). Earlier studies (Enstrom et al. 1992, Gey et al. 1993) suggested an inverse relationship between vitamin C intake and CHD risk, whereas large prospective observational studies have not been consistent (Jha et al. 1995). Three randomized trials have also yielded conflicting results (Jha et al. 1995). Thus, the independent effects of vitamin C intake on risk for CHD are unclear.

Although most attention has focused on antioxidants and decreased oxidation of LDL, various antioxidants have other vascular-protective effects. Prince et al. (1991) summarize the following effects of antioxidants that are unrelated to LDL oxidation: preservation of endothelial-derived nitric oxide action; inhibition of leukocyte adhesion; reduction of cellular oxidation damage; and inhibition of plalelet activation and smooth muscle proliferation.

The available data suggest strongly that vitamin E intake is associated with a protection from CHD. β-Carotene and vitamin C may also have protective effects. Further clinical trials are required to assess the clinical importance of these observations. Currently, at least eight prospective trials examining the effects of antioxidant vitamin supplementation on cardiovascular disease are in progress. These studies, individually or in aggregate, should have the numerical strength to provide more definitive answers to current questions regarding the relationship of antioxidant vitamin intake and CHD.

FERMENTATION OF DIETARY FIBER

Most dietary fibers are fermented in the colon to SCFA, methane, carbon dioxide and hydrogen (Pomare et al. 1985). Oligosaccharides and soluble fibers are almost completely fermented in the colon, whereas some insoluble fibers such as wheat bran are fermented only partially. Most starches and resistant fibers that reach the colon are fermented completely. Because of the different metabolic fates of SCFA and because of their different metabolic effects, they deserve attention for their potential health implications.

Acetate, propionate and butyrate are the principal SCFA produced in the human colon (Pomare et al. 1985). Simplis-

TABLE 2

Representative values for acetate (A), propionate (P), butyrate (B) and total short-chain fatty acid (SCFA) production (mmol/g of original organic matter) from different fiber sources

	Fiber free[1]	Cellulose[2]	Beet pulp[2]	Citrus pulp[2]	Citrus pectin[2]	Oligofructose[3]	Inulin[3]
Total SCFA		−0.04	4.76	5.43	5.56		
Acetate		−0.15	2.60	3.28	3.18		
Propionate		0.04	1.29	1.20	1.19		
Butyrate		0.07	0.87	0.95	1.19		
A:P:B Ratio	92:7:1		55:27:18	60:22:18	57:21.5:21.5	78:14:8	72:19:8

[1] Data from MacZulak et al. (1993).
[2] Data from Sunvold et al. (1995).
[3] Data from Wang and Gibson (1993).

tically, acetate traverses the liver and enters the peripheral circulation (Bridges et al. 1992). Propionate is extracted by the liver and affects lipid metabolism (Bridges et al. 1992). Butyrate appears to have health-promoting effects for colonocytes and only a portion of butyrate leaves the colon for extraction by the liver (Pomare et al. 1985). **Table 2** outlines SCFA production from different dietary fiber sources and supplies information on the ratio of the individual SCFA acetate, propionate and butyrate produced.

The acetate/propionate/butyrate ratios are affected by the substrate available to the bacterial flora of the colon. In free-living humans consuming a typical Western diet, this acetate/propionate/butyrate ratio of material in the colon is approximately 60:25:15. Starches tend to increase the relative amount of acetate, whereas some fibers, such as oat bran, tend to increase the relative amount of propionate.

MacZulak et al. (1993) used an animal model to study the effect of diets high in fiber on fecal microorganism output and microbial fermentation products. In these studies, the male Wistar rats were divided into groups of five and fed high fiber and fiber-free diets in varying order for a 3- to 4-wk period. The high fiber diet contained 40% soy cake, 20% crude potato starch, 19% wheat bran and 5% each of apple pectin and carob gum. The fiber-free diet contained 24% soy protein and 65% wheat starch. It was determined that total anaerobe fecal concentration was 70 times higher in the feces after consumption of the high fiber diet compared with that of the fiber-free diet. It appears that the high fiber diet provides substrates necessary for microbial fermentation and growth in the cecum. In addition, the high fiber diet influenced the proportion of organic acid products such that the acetate/proptionate/butyrate ratio was 69:21:10 with consumption of the high fiber diet vs. 92:7:1 with the fiber-free diet. These results represent an elevation in propionate and butyrate production when subjects consume a diet rich in fiber sources.

Sunvold et al. (1995) studied the in vitro fermentation characteristics of several fiber sources including cellulose, beet pulp, citrus pulp and citrus pectin. The fiber substrates were incubated for 6, 12, 24 and 48 h with human feces. Total SCFA production was greatest with citrus pectin, followed by citrus pulp, beet pulp and cellulose. The acetate/propionate/butyrate ratios after 48 h were 55:27:18 for the beet pulp, 60:22:18 for the citrus pulp and 57:21.5:21.5 for the citrus pectin. These results indicate that the source of dietary fiber does influence substrate fermentability by gut microflora in humans. In a similar trial, Wang and collaborators (Wang and Gibson 1993) studied the effects of the in vitro fermentation of inulin and oligofructose by bacteria growing in the human large intestine. Fermentation products were found from slurries of mixed human fecal bacteria. The acetate/propionate/butyrate ratio for inulin was 72:19:8 and for oligofructose was 78:14:8.

BIFIDOGENIC EFFECTS OF DIETARY FIBER

The *Bifidobacterium* species account for ~12–15% of the bacteria present in the human colon (Okubo et al. 1994, Salyers et al. 1985). Many health benefits have been attributed to the *bifidobacteria* (Hayakawa et al. 1990), and one goal of healthy nutrition is to increase *bifidobacteria* counts in the human colon. Intake of oligofructoses and inulin significantly increase the percentage and total counts of *bifidobacteria* in the human colon (Gibson et al. 1995). Because soluble dietary fibers such as oligofructoses and inulin are extensively fermented in the colon, they also have the potential to increase the *bifidobacteria* counts of the colon. Only limited information is available on the effects of soluble fibers on human colonic *bifidobacteria*.

In animals models, certain soluble fibers such as guar gum (a galactomannan polymer) significantly increase the *bifidobacteria* counts in the colon. It is possible that galactose, like fructose, selectively stimulates the growth of certain *bifidobacteria* species in the colon.

Okubo et al. (1994) examined the effects of intake of partially hydrolyzed guar gum (PHGG) on bacterial counts of feces from volunteer subjects fed control diets and diets containing PHGG. After a 2-wk control period, nine subjects consumed 7 g of PHGG in a beverage three times daily (21 g/d). The percentage of *bifidobacteria* in the feces increased from 14.7 to 31.7% after 1 wk and was 24.8% after 2 wk. Two weeks after discontinuing intake of PHGG, the *bifidobacteria* count of the fecal samples returned to pretreatment values. The *bifidobacteria* counts were significantly higher during wk 3 and 4 of PHGG ingestion than values at baseline or after cessation of PHGG intake. Of interest, *lactobacillus* counts also increased significantly with PHGG consumption, but significant changes were not observed in the concentrations of any other microflora.

CONCLUSION

Vegetables, fruits, whole-grain cereals and legumes are rich sources of nutrients, phytochemicals and antioxidants. These fiber-rich foods have been shown in animal, epidemiologic and clinical trials to be protective against CHD. Dietary fiber in particular exerts favorable effects on fasting and postprandial serum lipoproteins, which are surrogate markers for risk for CHD. In humans, psyllium and guar gum appear to be the most effective cholesterol-lowering soluble fibers. However,

wheat bran has a significant triglyceride-lowering effect, which may serve as an independent risk factor for ASCVD.

In addition to its effects on lipoproteins, dietary fiber also has a positive influence on blood pressure, obesity, insulin resistance and clotting factors, which are all independent risk factors for CHD. When evaluating the role of dietary fiber in ASCVD risk, one must also consider the non-fiber components of plant foods, including phytochemicals, antioxidant vitamins and certain (n-3) fatty acids. Available data strongly suggest that vitamin E intake is associated with a protection from CHD, and β-carotene and vitamin C may also have protective effects.

Like oligosaccharides, soluble fibers are almost completely fermented in the colon to SCFA, methane, carbon dioxide and hydrogen. The SCFA ratios of acetate/propionate/butyrate vary and are influenced by substrate availability to the bacterial flora of the colon. It is also of interest that dietary fiber, like oligofructoses and inulin, has the potential to increase the *bifidobacteria* counts of the colon. This elevation in *bifidobacteria* offers health benefits independent of those normally attributed to fiber-rich foods. Inclusion of dietary fiber in the diet offers benefits not only to the heart, but also to overall health.

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