Whole grains protect against atherosclerotic cardiovascular disease

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Atherosclerotic cardiovascular disease (ASCVD) is the most common cause of death in most Western countries. Nutrition factors contribute importantly to this high risk for ASCVD. Favourable alterations in diet can reduce six of the nine major risk factors for ASCVD, i.e. high serum LDL-cholesterol levels, high fasting serum triacylglycerol levels, low HDL-cholesterol levels, hypertension, diabetes and obesity. Wholegrain foods may be one the healthiest choices individuals can make to lower the risk for ASCVD. Epidemiological studies indicate that individuals with higher levels (in the highest quintile) of whole-grain intake have a 29 % lower risk for ASCVD than individuals with lower levels (lowest quintile) of whole-grain intake. It is of interest that neither the highest levels of cereal fibre nor the highest levels of refined cereals provide appreciable protection against ASCVD. Generous intake of whole grains also provides protection from development of diabetes and obesity. Diets rich in wholegrain foods tend to decrease serum LDL-cholesterol and triacylglycerol levels as well as blood pressure while increasing serum HDL-cholesterol levels. Whole-grain intake may also favourably alter antioxidant status, serum homocysteine levels, vascular reactivity and the inflammatory state. Whole-grain components that appear to make major contributions to these protective effects are: dietary fibre; vitamins; minerals; antioxidants; phytosterols; other phytochemicals. Three servings of whole grains daily are recommended to provide these health benefits.

Atherosclerotic cardiovascular disease: Whole grains: Dietary fibre

Atherosclerotic cardiovascular diseases (ASCVD), including CHD, cerebrovascular disease and hypertensive heart disease, are the most common cause of death in Western countries and account for about 40 % of all deaths (American Heart Association, 2000). Nutrition approaches to prevention are safer and more cost-effective than pharmacological approaches. Jenkins et al. (2000) recently summarized nutrition approaches to decreasing serum LDL-cholesterol values, which is a major risk factor for CHD. These nutrition interventions, that have the potential to decrease serum LDL-cholesterol values by 35 %, include: low-saturated fat low-cholesterol diets; increased intake of soluble fibre; increased intake of soyabean protein; intake of plant sterols (Jenkins et al. 2000). Recent epidemiological evidence also indicates that higher intakes, when compared with lower intakes, of wholegrain foods are associated with lower risk for CHD (Anderson et al. 2000b).

The intake of wholegrain foods by adults in the USA and in Europe appears to be less than one serving per d, far below the recommended intake of three servings per d (Cleveland et al. 2000). The available clinical data suggest that adults would gain appreciable protection from CHD by consuming the recommended three servings of whole grains daily (Anderson et al. 2000b). Health claims for whole grains have been approved in the USA and UK. Wholegrain foods are rich sources of many nutrients and phytochemicals, including: complex carbohydrates; dietary fibre; resistant starch; oligosaccharides; minerals; n-3 fatty acids; vitamins; antioxidants; other phytochemicals (Slavin et al. 1997; Anderson et al. 2000b). The components that contribute to the health benefits have not been clearly identified and the mechanisms are poorly understood.

The present paper will specifically examine the strength of the association between whole grains and protection from ASCVD, contrast the effects of whole-grain intake v. refined-grain intake, and review proposed effects of whole grains on risk factors for CHD.
Atherosclerotic cardiovascular disease

Strong evidence supporting the high-fibre food–CHD hypothesis first emerged clearly from the report of Morris et al. (1977). They observed that working men in the UK who had the highest intakes of cereal fibre had 80 % lower rates of heart attacks than those with the lowest intake of cereal fibre. These observations have been confirmed and extended by a number of other investigators (Anderson et al. 2000b).

Four studies have critically examined the association between whole-grain food intake and risk for CHD (Fraser et al. 1992; Jacobs et al. 1998, 1999; Liu et al. 1999). In addition, one study examined the association between whole-grain intake and ischaemic stroke (Liu et al. 2000). Previously, all the available controlled studies were tabulated to compare the effects of whole-grain intake with that of cereal fibre, total dietary fibre, and fruit and vegetable intakes on risk for CHD (Anderson et al. 2000b). The results of twenty-four controlled studies were tabulated and a meta-analysis was performed for the studies that provided adequate data for analysis. This earlier tabulation has been updated and the results are summarized in the present paper.

Methods

To appraise the literature, research reports that met the following criteria were identified: (1) inclusion of some dietary measure related to whole-grain, fibre or food intake; (2) reporting of outcome data related to CHD events; (3) presentation of an estimate of variance so that variance-adjusted calculations could be made (Anderson et al. 2000b). Thirty studies met the inclusion criteria and are included in the summary estimates provided in Table 1. Six of these studies did not provide sufficient data to calculate effect estimates. Four studies specifically reported on whole-grain intake and one study reported on wholewheat bread intake and was included in the whole-grain analysis (Fraser et al. 1992; Jacobs et al. 1998, 1999; Liu et al. 1999, 2000). Additional studies provided data on cereal fibre, total dietary fibre, and fruit and vegetable intakes (Anderson et al. 2000b). CHD events, CHD deaths or ischaemic strokes were assessed as the primary outcome measures.

Thirteen studies provided sufficient data and were appropriate for the meta-analysis calculations. Variance-adjusted event rates and 95 % CI were calculated using fixed-effect model assumptions. All analyses were performed using SAS-PC version 6.12 (SAS Institute Inc., Cary, NC, USA), as previously described (Anderson et al. 2000b).

Results

Seven of eight reports assessing whole-grain intake and risk for ASCVD reported a negative association and six (75 %) noted a significant negative association (Table 1). Seven of eight reports assessing cereal-fibre intake and risk for CHD reported a negative association and fourteen (82 %) noted a significant negative association. Sixteen of seventeen reports assessing total fibre intake and risk for CHD reported a negative association and fourteen (82 %) noted a significant negative association. Nine of eleven reports assessing fruit intake and risk for CHD reported a negative association but only two (18 %) noted a significant negative association. Finally, eleven of eleven reports assessing vegetable intake and risk for CHD reported a negative association and five (46 %) noted a significant negative association. Thus, in this semi-quantitative analysis total dietary fibre and whole-grain intakes show the strongest negative association with CHD events.

Results from the thirteen studies suitable for meta-analysis are presented in Table 2. These values were computed using values reported after secondary adjustment for covariates such as smoking, BMI, hypertension, supplement use and other factors, as detailed previously (Anderson et al. 2000b). Again, total dietary fibre and whole-grain intakes were associated with the greatest protection from CHD events. The risk ratio for whole grains comparing the lowest and highest groups of whole-grain intake was 0·71 (95 % CI 0·48, 0·94) indicating that whole grains were associated with a significant reduction in risk approximating to 29 %. In sharp contrast, cereal fibre was not associated with a significant reduction in risk, having a risk ratio of 0·9 (95 % CI 0·8, 1·01). The risk reduction for CHD associated with total dietary fibre intake was 0·73 (95 % CI 0·73, 0·83); these values were virtually identical to those for whole-grain intake. Fruit intake was associated with a risk reduction of 0·77 (95 % CI 0·70, 0·86) and vegetable intake was associated with a risk ratio of 0·86 (95 % CI 0·77, 0·96).

Discussion

This meta-analysis of multiple studies confirms and strengthens the observations of the individual studies suggesting that whole grains may have more protective action against CHD than other foods commonly eaten by...
North Americans and Europeans. Whole-grain intake appears to be slightly more protective than fruit or vegetable intakes. The protection associated with whole-grain intake is virtually identical to that provided by total dietary fibre. It is of interest that this analysis indicates that cereal fibres are not associated with a substantial protective effect. This finding appears to be questionable until it is noted that the endosperm of most grains is rich in hemicelluloses but has minimal levels of phytochemicals (MacDougall & Selvendran, 2001). Most antioxidants, phytosterols and other phytochemicals are concentrated in the bran or germ of most cereals (Slavin et al. 1997; Miller et al. 2000).

**Whole-grain v. refined-grain intake and atherosclerotic cardiovascular disease**

Neither cereal fibre intake nor refined-grain intake appears to provide the protection from ASCVD that is reported for whole-grain intake. Our meta-analysis indicated that cereal fibre had a negative association with CHD risk which did not reach statistical significance (Anderson et al. 2000b). Reports from both the Iowa Women’s Health Study and the Nurses’ Health Study indicate that whole-grain intake has a significant negative association with CHD or ischaemic stroke whereas refined-grain intake does not appear related (Jacobs et al. 1999; Liu et al. 2000). Jacobs et al. (1999) noted that women with the highest quintile for whole-grain intake had a reduction in CHD by 14% \(P=0.005\) compared with the lowest quintile. However, women with the highest level of refined-grain intake had a 9% increase in CHD risk \(P=0.7\) compared with women with the lowest level. Liu et al. (2000) reported that women with the highest level of whole-grain intake had a 31% lower risk \(P=0.08\) for ischaemic stroke than women with the lowest level of intake. However, women with the highest level of refined-grain intake had ischaemic strokes at the same rate as women with the lowest intake.

The differences in CHD risk associated with different parts of the cereal grain may relate to differences in the composition and constituents of the dietary fibre. Refined grain products contain only the endosperm (starch and hemicelluloses) while wholegrain products include the endosperm, bran layer and germ. The bran layer and germ are rich in dietary fibre, phytochemicals and other components that may provide cardiovascular protection (MacDougall & Selvendran, 2001).

**Effects on risk factors**

Some of the major risk factors for CHD that are reversible include: increased LDL-cholesterol levels; high fasting serum triacylglycerols; low HDL-cholesterol values; hypertension; diabetes; obesity; lack of exercise; poor stress management; cigarette smoking (Anderson et al. 1990; Kannel, 1996; Krauss et al. 2000). The first six of these major risk factors may be favourably altered by dietary intervention. The following risk factors are emerging as important considerations for their role in CHD: low antioxidant vitamin status (Jha et al. 1995); hyperhomocysteinaemia (Welch & Loscalzo, 1998); evidence of an inflammatory state (Ross, 1999). Whole grains have the potential to favourably alter the following risk factors:

- Elevated serum LDL-cholesterol values; hypertriacylglycerolaemia; decreased serum LDL-cholesterol values; hypertension; diabetes; obesity; insulin resistance; suboptimal antioxidant status; hyperhomocysteinaemia; altered vascular reactivity; the inflammatory state. These areas will be reviewed to discuss the potential benefits of whole-grain intake.

**Abnormalities of LDL-cholesterol**

Changes in serum levels, particle size and oxidation of LDL appear to play a central role in the pathogenesis of atherosclerosis. Abnormalities of this particle may be the single greatest risk factor for atherosclerotic disease in Western populations (Navab et al. 1996). Wholegrain oat products are particularly effective in decreasing serum LDL-cholesterol concentrations (Anderson & Gustafson, 1988; Ripsin et al. 1992). Wholegrain barley products also effectively decrease serum LDL-cholesterol values (McIntosh et al. 1991). While less potent, wheat products with moderate amounts of soluble fibre have LDL-cholesterol-lowering properties (Anderson et al. 1991a). Whole grains appear to exert some of, but not all, their protective effects to reductions in serum LDL-cholesterol values (Truswell, 2002).

**Hypertriacylglycerolaemia**

Elevations in serum triacylglycerols values reflect a substantial increase in risk for CHD, but whether the triacylglycerol-rich particles carry the risk or simply serve as markers for a constellation of other risk factors such as insulin resistance is unclear (Ginsberg, 1997). Elevations in fasting triacylglycerols may reflect a derangement of lipoprotein metabolism as well as lipoprotein particle size and composition that increase risk through poorly understood mechanisms (Rubins et al. 1999; Anderson, 2000). Since Zilversmit (1979) advanced the hypothesis relating postprandial lipaemia to atherosclerosis, this area has been extensively investigated. Most of the epidemiological data indicate a positive association between fasting serum triacylglycerols and CHD risk (Ginsberg, 1997). The effects of diet on fasting serum triacylglycerols are also controversial. While replacing dietary fat with carbohydrate usually increases fasting serum triacylglycerol values (Park & Hellerstein, 2000), an increase in dietary carbohydrate and fibre at the expense of dietary fat does not affect triacylglycerol levels (Anderson, 2000). Furthermore, decreasing dietary fat intake and increasing dietary carbohydrate intake decreases postprandial hypertriacylglycerolaemia (Anderson et al. 1980). A recent clinical trial confirmed the effects of dietary fibre in decreasing fasting serum triacylglycerol values (Chandalia et al. 2000). Thus, several careful studies indicate that increased intake of whole grains is likely to decreases fasting and postprandial serum triacylglycerol values (Anderson et al. 1980, 1991b; Anderson, 2000; Chandalia et al. 2000).

**Low HDL-cholesterol**

Alterations in HDL levels or function may be the second most important lipoprotein disturbance linked to CHD.
(Gowri et al. 1999; Rubins et al. 1999). Dietary fibres usually have a neutral effect on serum HDL-cholesterol values (Olson et al. 1997; Brown et al. 1999; Anderson et al. 2000a). Psyllium intake may increase apolipoprotein A-I, a protective component of HDL (Anderson et al. 2000a). Intake of soyabean protein tends to increase serum HDL-cholesterol values slightly but not significantly (Anderson et al. 1995). While not carefully examined, it seems probable that increased intake of whole grains would increase HDL concentrations and favourably affect function (Fung et al. 2001).

Hypertension

The three most important risk factors for CHD appear to be hypercholesterolaemia, cigarette smoking and hypertension; these factors are sometimes referred to as the ‘Big Three’ (Anderson et al. 1990; Kannel, 1996). Early clinical research with dietary fibre showed a reduction in blood pressure when diabetic individuals were placed on high-fibre high-carbohydrate diets (Anderson, 1983). Subsequent studies reported that high fibre intakes reduced blood pressure (Anderson, 1995). Limitations of these studies relate to the fact that high-fibre foods are higher in complex carbohydrate and fibre and lower in fat than control foods. Fibre supplements may not mimic the effects of whole foods in these clinical studies. A careful meta-analysis of the evidence indicates that increasing dietary fibre intake with body-weight maintenance is associated with a small, but statistically significant, reduction in blood pressure (He & Whelton, 1999). Additional epidemiological evidence also supports the protective role for fibre with respect to hypertension (Ascherio et al. 1992).

A landmark clinical trial, the Dietary Approaches to Stop Hypertension, encouraged a healthy diet including vegetables, fruits and whole grains (Appel et al. 1997). While rich in K, Mg and Ca, this diet was also generous in dietary fibre. For non-hypertensive individuals this diet decreased systolic and diastolic blood pressure by 3.5 and 2.1 mmHg respectively. Reductions in blood pressure in hypertensive individuals were substantially greater. This important study, the findings of which were subsequently confirmed, emphasizes the benefits of dietary interventions in the first-line treatment of hypertension (Sacks et al. 2001). It seems probable that the increased intake of whole grains would slow the development of hypertension and lower blood pressure in hypertensive individuals.

Diabetes

Diabetes was recently upgraded to a major risk factor for CHD joining the ‘Big Three’ (Krauss et al. 2000). Dietary fibre and whole-grain intake protect from development of diabetes and, furthermore, improve glycaemic management in diabetic individuals. As reviewed by Anderson & Akanji (1991), the initial clinical research with dietary fibre focused on its effects for individuals with diabetes. Subsequently, the Anderson team (Anderson & Akanji, 1991) utilized diets rich in high-fibre foods and whole grains to show dramatic improvement in glycaemic control with marked decreases in insulin or oral medication requirements for diabetic individuals. Concurrently, Vinik & Jenkins (1988) utilized fibre supplements in diabetic individuals. Vinik and Jenkins (1988) showed that taking fibre supplements with meals markedly reduced post-prandial hyperglycaemia. The observations led to the ‘glycaemic index’ concept. The glycaemic index, of course, is affected by fibre and by many other characteristics of the meal (Jenkins et al. 1981). In combination these studies established the important role of dietary fibre in the management of diabetes (Anderson, 1999). Recent studies confirm the benefits of dietary fibre for individuals with diabetes (Anderson et al. 1999a; Chandalia et al. 2000).

Recent observational studies indicate that a high fibre intake is associated with a marked reduction in the prevalence of diabetes (Salmeron et al. 1997a,b; Meyer et al. 2000). More specifically, Meyer et al. (2000) reported that the highest quintile of whole-grain intake was associated with a significant reduction (21 %, P=0.0089) in risk for developing diabetes. These data are supported by clinical studies indicating that whole-grain intake increases insulin sensitivity (Pereira et al. 2002) and has a favourable impact on gut-hormone and insulin responses after meals (Juntunen et al. 2000). It seems probable that increased intake of whole grains would decrease the prevalence of diabetes and improve blood glucose management in diabetic individuals.

Obesity

Obesity has not been given the attention it deserves as an independent risk factor for CHD (Manson et al. 1995; Anderson & Konz, 2001). For approximately 30 years epidemiological data, observational studies, human experimental research and clinical trials support a role for dietary fibre in the development and management of obesity (Anderson & Bryant, 1986). For example, a recent observational study reported that individuals with higher fibre intakes had markedly lower rates of obesity than individuals with lower fibre intakes (Ludwig et al. 1999). Many clinical trials suggest a role for dietary fibre in the management of obesity, but the data are not conclusive. The use of blinding in clinical trials involving high-fibre foods has not been possible and placebo effects may have contributed to favourable outcomes. Since the early study of Mickelsen et al. (1979) demonstrating the weight-reducing benefits of high-fibre bread, many clinical studies have reported weight-loss benefits from increasing fibre intake (Anderson & Siesling, 1980; Duncan et al. 1983; Anderson, 1985; Russ & Atkinson, 1985). Thus, the available data, while not conclusive, strongly indicate that dietary fibre may offer substantial benefits in the clinical management of obesity. It seems probable that increased intake of whole grains would decrease the risk for developing obesity, have a beneficial role in weight management and, thereby, decrease risk for ASCVD.

Insulin resistance

The insulin resistance syndrome is emerging as a major contributor to risk for CHD. Insulin resistance is characterized
by hyperinsulinaemia, hypertriacylglycerolaemia and low HDL-cholesterol concentrations, and affects about 47 million adults in the USA (Ford et al. 2002). Commonly-associated features are visceral adiposity, hypertension and glucose intolerance or diabetes (Reaven, 1988; Anderson & Hanna, 1999). Hyperinsulinaemia, itself, may be an independent risk factor for CHD, although many researchers consider it a marker for the insulin resistance syndrome (Despres et al. 1996). As reviewed elsewhere, high fibre intakes decrease hyperinsulinaemia, decrease insulin resistance and combat this hazardous syndrome (Anderson & Hanna, 1999). Our previous studies indicate that high carbohydrate intakes together with high fibre intakes decrease insulin requirements in diabetic individuals (Anderson et al. 1999b) and increase sensitivity to insulin for non-diabetic individuals (Fukagawa et al. 1990). Pereira et al. (2002) recently reported that short-term increases in the intake of whole grains increased insulin sensitivity of overweight hyper-insulinaemic adults. The mechanism responsible for this improvement in insulin sensitivity is unclear. Thus, it seems probable that increased whole-grain intake would improve insulin sensitivity and decrease risk for CHD for hyperinsulinaemic individuals, but more research is required in this area.

Sub-optimal antioxidant status

Low intakes of antioxidant vitamins, especially vitamin E, appear to be associated with high risk for CHD (Gey et al. 1993; Rimm et al. 1993; Stampfer et al. 1993; Reginstrom et al. 1996). These observations are consistent with the hypothesis that oxidation of LDL has a major role in the pathogenesis of atherosclerosis (Navab et al. 1996; Anderson et al. 1999b). However, intervention trials utilizing antioxidant vitamin supplements are not conclusive (Jha et al. 1995). In fact, recent studies suggest that vitamin E may diminish the protective effects of hypocholesterolaemic ‘statins’ drugs when the two supplements are administered concurrently (Brown et al. 2001). Nevertheless, whole grains are excellent sources of antioxidant vitamins and phytochemicals and may protect from CHD through these substances (Miller et al. 2000).

Hyperhomocysteinaemia

Homocysteine, an S-containing amino acid, has a variety of toxic effects on the vascular endothelium and also increases risk for thrombosis (Welch & Loscalzo, 1998). McCulloch (1969) noted that hyperhomocysteinaemia was associated with severe atherosclerotic vascular disease. Subsequent epidemiological studies have reported a strong association between serum homocysteine levels and CHD and cerebral vascular disease (Kang et al. 1992; Boushey et al. 1995; Selhub et al. 1995; Stamper & Malinow, 1995). Sub-optimal intakes of folic acid, pyridoxine and cobalamin are associated with higher serum homocysteine levels, and supplementation with these vitamins decreases serum levels (Welch & Loscalzo, 1998). Intake of wholegrain products, especially those fortified with water-soluble vitamins (Boushey et al. 1995), would also act to reduce serum homocysteine levels and decrease risk for ASCVD (Boushey et al. 1995; Jacques et al. 1999).

Altered vascular reactivity

While favourable lipid profiles protect premenopausal women from CHD, new evidence suggests that effects of oestrogen on vascular reactivity may have an even greater protective effect for CHD (Reis et al. 1994; Subbiah, 1998; Mendelsohn & Karas, 1999). Oestrogens bind to specific intracellular receptors and protect blood vessels from injury and atherosclerosis. These hormones promote appropriate vasodilatation of coronary arteries when increased blood supply is required (Mendelsohn & Karas, 1999). Soyabean isoflavones, potent agonists of β-oestrogen receptors in blood vessels, appear to act in a similar manner to mammalian oestrogens (Honore et al. 1997; Williams & Clarkson, 1998). Preliminary studies suggest that soyabean isoflavones have similar effects on peripheral blood vessels in human subjects (Nestel et al. 1997). Whole grains also provide phyto-oestrogens that are likely to have similar protective effects on blood vessels (Slavin et al. 1997). Thus, it seems probable that phyto-oestrogens from whole grains have a protective effect on vascular reactivity and reduce risk for vascular events related to arterial spasm.

Increased inflammatory state

Recent research reinforces the role of inflammation in the pathogenesis of atherosclerosis (Ross, 1999). Some of the evidence linking inflammation to atherosclerosis is summarized as follows: histological evidence of inflammation in atherosclerotic plaques; increased levels of thromboxanes and leukotrienes; activated circulating leukocytes; increased serum concentrations of C-reactive protein (Albert et al. 2002). Soyabean isoflavones, more extensively studied than similar phyto-oestrogens (lignans) from whole grains (Slavin et al. 1997), have a number of anti-inflammatory actions. Isoflavones inhibit adhesion molecule expression, alter arachidonic acid metabolism, inhibit oxygen radical generation and inhibit chemotactic factor production (Sadowska-Krowicka et al. 1998; Regal et al. 2000). These isoflavones demonstrate anti-inflammatory potential in a number of animal models such as chronic ileitis, inflammation-induced corneal neovascularization and ischaemic reperfusion injury (Regal et al. 2000). Emerging evidence suggests that soyabean isoflavones may inhibit some of the cellular processes contributing to the atherosclerotic lesion (Raines & Ross, 1995). The potential role of lignans in whole grains in reducing inflammation as it relates to protection from CHD requires further study.

Other factors

Minor components of whole grains, including n-3 fatty acids and certain minerals (e.g. Zn, Cr and Mg), may also contribute to their protective effect for CHD (Slavin et al. 1997). Soyabean isoflavones exert anti-thrombotic and anti-platelet aggregating effects (Wilcox & Blumenthal, 1995). Since thrombus formation precedes most myocardial infarction, decreasing platelet aggregation and thrombo-
genesis could protect from these events. Whole-grain phytochemicals are likely to have similar anti-platelet aggregating and anti-thrombotic effects (Slavin et al. 1997).

Conclusions

Whole grains are among the healthiest food choices that individuals make. These foods are rich in fibre and phytochemicals and have a wide variety of health benefits. Recently, health claims suggesting that whole-grain intake may reduce risk for CHD were approved in the USA and the UK. The US Department of Agriculture recommended that all individuals consume three servings of whole grains daily. Whole-grain intake appears to protect from development of CHD and diabetes. The emerging science regarding health benefits and mechanisms strongly supports these nutrition guidelines.

References


Circulation 105, 2595–2599.


