

The cardiovascular effects of flaxseed and its omega-3 fatty acid, alpha-linolenic acid

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Preventing the occurrence of cardiovascular disease (CVD) with nutritional interventions is a therapeutic strategy that may warrant greater research attention. The increased use of omega (ω)-3 fatty acids is a powerful example of one such nutritional strategy that may produce significant cardiovascular benefits. Marine food products have provided the traditional dietary sources of ω -3 fatty acids. Flaxseed is an alternative to marine products. It is one of the richest sources of the plant-based ω -3 fatty acid, alpha-linolenic acid (ALA). Based on the results of clinical trials, epidemiological investigations and experimental studies, ingestion of ALA has been suggested to have a positive impact on CVD. Because of its high ALA content, the use of flaxseed has been advocated to combat CVD. The purpose of the present review was to identify the known cardiovascular effects of flaxseed and ALA and, just as importantly, what is presently unknown.

Key Words: Cardiovascular disease; Fibre; Fish; Heart disease; Lignans; Nutrition; Polyunsaturated fatty acids

Coronary artery disease (CAD) is a leading cause of death today and a major economic challenge for the health care system (1,2). There are now significant research data suggesting that CAD can be altered or prevented in large part by three major lifestyle changes. These three factors are nutritional modification, incorporating exercise into our daily lives and eliminating smoking (3). The implementation of only one of these three factors – nutritional modification – may generate significant effects on CAD. For example, increasing the consumption of omega (ω)-3 fatty acids may be a particularly powerful dietary strategy to combat CAD (4,5). Consumption of ω -3 polyunsaturated fatty acids (PUFAs) is usually in the form of marine oils from fish. Fish oil contains both docosahexaenoic acid (DHA, C22:6 ω -3) and eicosapentaenoic acid (EPA, C20:5 ω -3). There is strong scientific evidence from human trials that ω -3 fatty acids from fish or fish oil supplements (EPA and DHA) can significantly reduce risk factors for heart disease (such as reducing blood triglyceride [TG] levels) (6-8), reduce the risk of nonfatal and fatal myocardial infarctions, sudden death and all-cause mortality (9-11), and produce small reductions in blood pressure (12-14) and platelet aggregation, and the thrombotic complications associated with platelet aggregation (9-11). Despite the data supporting the contention that the long-chain ω -3 fatty acids EPA and DHA in fish oil have significant, beneficial cardiovascular potential, dietary endorsement has not been widespread. Concerns about fish taste, smell, toxin content, allergies and eructation following a fish meal are some of the factors that have limited their dietary use.

FLAXSEED AS A SOURCE OF ω -3 FATTY ACID

Recently, flaxseed (linseed) was identified as an alternative plant source of ω -3 fatty acids. The ω -3 fatty acids found in flaxseed differ from those

Les effets cardiovasculaires des graines de lin et de ses acides gras oméga 3, l'acide alpha-linolénique

La prévention de l'occurrence de maladies cardiovasculaires (MCV) au moyen d'interventions nutritionnelles est une stratégie thérapeutique qui pourrait susciter plus de recherches. L'utilisation accrue d'acides gras oméga (ω)-3 est un exemple évocateur de stratégie nutritionnelle qui peut procurer des bienfaits cardiovasculaires. Les produits alimentaires marins ont toujours constitué la source alimentaire d'acides gras ω -3. Les graines de lin peuvent toutefois remplacer les produits marins. C'est l'une des sources les plus riches d'acides gras ω -3 d'origine végétale, l'acide alpha-linolénique (ALA). Selon les résultats d'essais cliniques, d'études épidémiologiques et d'études expérimentales, il est postulé que l'ingestion d'ALA aurait des effets positifs sur les MCV. En raison du contenu élevé des graines de lin en ALA, on avance que son utilisation combat les MCV. La présente analyse visait à déterminer les effets cardiovasculaires connus des graines de lin et de l'ALA et, de manière tout aussi importante, ceux qu'on ne connaît pas encore.

in fish (Figure 1). Flaxseed is one of the richest plant sources of the ω -3 fatty acid alpha-linolenic acid (ALA, C18:3 ω -3) (15), but it is found in other foods as well (Table 1). The typical North American diet provides approximately 1.4 g of ALA per day, and 0.1 g to 0.2 g of EPA and DHA (16). ALA can be converted to long-chain ω -3 PUFA. In a cross-study meta-regression analysis (17) of plasma phospholipid ω -3 fatty acid concentrations after ALA supplementation, it was observed that ALA supplementation with up to 14 g/day resulted in dose-dependent but modest increases in plasma ALA concentrations. Some of the observed variability, especially at low ALA doses, was attributed to differences in the amount of n-6 PUFA linoleic acid (LA) concurrently administered in the diet. The dose response appeared linear ($r^2=0.79$, $P=0.008$). There were small increases in EPA after ALA supplementation ($r^2=0.49$, $P=0.052$); however, plasma phospholipid DHA concentrations did not detectably increase in this study.

Current dietary recommendations for adults suggest a daily intake of 2.22 g of ALA based on a 2000 kcal diet (18). Ingesting flaxseed can provide ALA to the circulation and tissues of the body. ALA levels are increased as early as two weeks after the initiation of flaxseed supplementation (19). The bioavailability of ALA is dependent on the type of flax ingested (ALA has greater bioavailability in oil than in milled seed, and has greater bioavailability in milled seed than in whole seed) (20). Crushing and milling of flaxseed substantially improve the bioavailability of enterolignans (21), likely due to the improved accessibility of the colon bacteria to crushed and ground flaxseed, the dose of flaxseed ingested (17) and the fat composition of the diet. For example, concurrent administration of LA in the diet will reduce ALA accumulation (17) because there is a competition among the enzymes involved in the elongation and desaturation of LA and ALA

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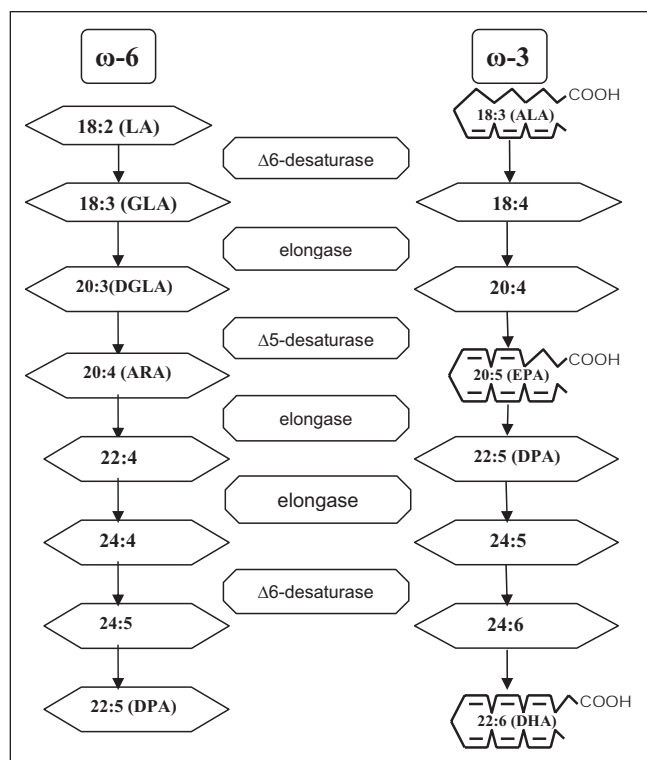


Figure 1 Interconversion of omega (ω)-6 and ω -3 fatty acids. Biochemical pathway. Δ Delta; ALA Alpha-linolenic acid; ARA Arachidonic acid; DGLA Dihomo-gamma-linolenic acid; DHA Docosahexaenoic acid; DPA Docosapentaenoic acid; EPA Eicosapentaenoic acid; GLA Gamma-linolenic acid; LA Linoleic acid

(Figure 1). A ratio of LA to ALA of 4:1 or lower has been shown to be optimal for the elongation of 11 g ALA to 1 g long-chain ω -3 PUFA (22). The age of the subject does not appear to influence ALA bioavailability or its conversion to DHA (23). The relative bioavailability of enterolignans from flaxseed does not differ in men versus women (21). Approximately 4 g of ALA appears to have biological effects similar to those of 0.3 g of long-chain ω -3 PUFA. Comparatively, EPA and DHA are more rapidly incorporated into plasma and membrane lipids, and produce more rapid effects than ALA. Therefore, the role of ALA in human nutrition may be more important in terms of long-term dietary intake (18).

EFFECTS OF FLAXSEED AND ALA INGESTION ON PRIMARY CARDIOVASCULAR END POINTS

Myocardial infarction, morbidity and mortality

If the two ω -3 PUFAs present in fish (EPA and DHA) are structurally different from the ALA found in flaxseed (24), their effects on CAD may be different as well. Unfortunately, data on the impact of the ALA found in flaxseed is not as well known or as mature as the fish data, and the health-related value of ALA or flaxseed has been debated (25-27).

Nine major studies (4,28-35) have reported that ALA levels are inversely correlated with primary cardiovascular events. The results are persuasive because most of these studies gathered data from large sample populations and/or over relatively long collection periods (multiple years) (Table 2).

More evidence that dietary ALA has significant cardioprotective efficacy has been demonstrated in secondary prevention trials. In the Lyon Diet Heart Study (36), ALA was associated with a decreased risk of recurrent fatal and nonfatal myocardial infarction, and a 73% reduction in risk of primary end points (cardiac mortality and morbidity) between the experimental and control groups. In a double-blinded,

TABLE 1
Selected sources of alpha-linolenic acid (ALA) and content of ALA in selected novel sources of omega-3 polyunsaturated fatty acids

Source of ALA*	ALA content, g
Pumpkin seeds (1 tbsp)	0.051
Olive oil (1 tbsp)	0.103
Walnuts, black (1 tbsp)	0.156
Soybean oil (1 tbsp)	1.231
Rapeseed oil (1 tbsp)	1.302
Walnut oil (1 tbsp)	1.414
Flaxseeds (1 tbsp)	2.350
Walnuts, English (1 tbsp)	2.574
Flaxseed oil (1 tbsp)	7.249
Almonds (100 g)	0.4
Peanuts (100 g)	0.003
Beans, navy, sprouted (100 g)	0.3
Broccoli, raw (100 g)	0.1
Lettuce, red leaf (100 g)	0.1
Mustard (100 g)	0.1
Purslane (100 g)	0.4
Spinach (100 g)	0.1
Seaweed, spirulina, dried (100 g)	0.8
Beans, common, dry (100 g)	0.6
Chickpeas, dry (100 g)	0.1
Soybeans, dry (100 g)	1.6
Oats, germ (100 g)	1.4
Rice, bran (100 g)	0.2
Wheat, germ (100 g)	0.7
Avocados, California, raw (100 g)	0.1
Raspberries, raw (100 g)	0.1
Strawberries, raw (100 g)	0.1
Novel sources of ALA†	ALA content, g
Breads and pasta (100 g)	0.1–1.6
Cereals (and granola bars) (55 g)	1.0–4.9
Eggs (50 g or 1 egg)	0.1–0.6
Processed meats (100 g)	0.5
Salad dressing (14 g – 31 g)	2.0–4.0
Margarine spreads (10 g – 100 g)	0.3–1.0
Nutrition bars (50 g)	0.1–2.2

1 tablespoon (tbsp) oil = 13.6 g; 1 tbsp seeds or nuts = 12.35 g. *Adapted from references 15 and 26; †Adapted from reference 27

placebo-controlled study (37) conducted in India, 120 patients with suspected acute myocardial infarction were followed and supplemented with 2.9 g/day of ALA (enriched oil). After one year of follow-up, both cardiac death and nonfatal myocardial infarction were significantly lower in this group of patients compared with those on placebo.

Work from animal studies may provide mechanistic insight. Atherosclerosis was significantly prevented by flaxseed supplementation in the hypercholesterolemic rabbit (38) and in the cholesterol-fed, low-density lipoprotein (LDL) receptor-deficient mouse (39) (Figure 2). Because there was a poor correlation between the progression of atherosclerotic lesions and the cholesterol-lowering effect of dietary flaxseed, the hypolipidemic effect of flaxseed is, at best, likely to be only one of the contributing factors to its antiatherogenic potential. Flaxseed (0.4 g/day) effectively inhibited the expression of inflammatory markers such as interleukin (IL)-6, mac-3, vascular cell adhesion molecule (VCAM)-1 and the proliferative marker proliferating cell nuclear antigen in aortic atherosclerotic tissue from LDL receptor-deficient mice (39). It was concluded that an important antiatherogenic role of ALA may involve a potent anti-inflammatory

TABLE 2
Investigations reporting effects of alpha-linolenic acid (ALA) on primary cardiovascular end points

Reference	Population (sample size)	Follow-up, years	Main results
Hu et al (28)	76,283 women	10	Higher intake of ALA provided significant protection against fatal myocardial infarction
Albert et al (29)	76,763 women	18	Inverse association between ALA and the risk of sudden cardiac death. Highest intakes of ALA obtained a 40% lower risk for sudden cardiac death
Erkkilä et al (4)	415	5	The content of ALA in the cholesteryl ester fraction, but not in phospholipids, tended to be associated with a reduced risk of death in patients with CAD
Baylin et al (30)	964	–	Inverse relationship between ALA in adipose tissue and nonfatal acute myocardial infarction
Oda et al (31)	157	–	Serum levels of ALA, EPA, DHA and total omega-3 polyunsaturated fatty acid were significantly lower in patients with acute myocardial infarction compared with the control group
Djoussé et al (32)	2004 white men and women	–	ALA-rich diet is associated with a lower prevalence of calcified atherosclerotic plaque in the coronary arteries
Djoussé et al (33)	4584 white men and women	–	A higher intake of ALA was inversely related to the prevalence OR of CAD by up to 40%. The reduction in the risk of CAD appeared to be independent of fish consumption
Ascherio et al (34)	43,757 men	6	A 1% increase in ALA intake (as % of energy) resulted in a 40% lower risk of nonfatal CAD
Dolecek (35)	12,866 men	6–8	Association between a high intake of ALA and a decreased risk of death from cardiovascular disease, CAD and all causes of death combined

CAD Coronary artery disease; DHA Docosahexaenoic acid; EPA Eicosapentaenoic acid

action. This is supported in clinical work. It is now well recognized that infectious disease and inflammation are important contributory factors to atherosclerotic CAD (40,41). Two independent studies of healthy subjects have shown that inflammatory markers, such as tumour necrosis factor- α (TNF- α), IL-1- β , thromboxane B₅ and prostaglandin E₅, were significantly reduced after administration of an ALA-rich diet (13.7 g/day of ALA from flaxseed) (42), as were VCAM-1 and E-selectin after delivery of 2 g/day of ALA (43). ALA intake (8 g/day) from a flaxseed source decreases serum concentrations of serum amyloid A, IL-6 (44,45), soluble VCAM-1, soluble intercellular adhesion molecule-1, soluble E-selectin (46) as well as the production of TNF- α , IL-1- β and prostaglandin E₂ by peripheral blood mononuclear cells (42) over a period of four to 12 weeks with doses of ALA greater than 9 g/day.

In a cross-sectional study, Djoussé et al (47) found that a higher intake of dietary ALA (highest tertiles 0.89 g/day) was inversely associated with heart rate-adjusted QT and JT intervals in a dose-response manner in both men and women. The authors suggested that dietary ALA might be associated with a reduced risk of abnormally prolonged repolarization. This is supported by animal work. Rabbits fed flaxseed exhibited a shorter QT interval than the controls, whereas the longest QT intervals were measured in the cholesterol-fed group (48). QT prolongation is associated with arrhythmias (49,50). The addition of flaxseed to the cholesterol-supplemented diet significantly shortened the QT interval in these hearts. Shortening of the QT interval was associated with a marked reduction in ventricular fibrillation in the flax-fed and the cholesterol plus flax-fed groups. Flaxseed, therefore, appears to exert its protective effect by shortening the QT interval and the action potential duration of the heart (48). It was suggested that alterations in Na⁺/Ca²⁺ exchange and action potential characteristics contributed to the antiarrhythmic action of flaxseed (48,51). The ALA content of flaxseed was also suggested to be the primary component within flaxseed that provided the antiarrhythmic action (48). This antiarrhythmic action may explain the lower incidence of sudden death in subjects ingesting ALA (29).

Stroke

Data collected from 1575 participants in the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study (52) showed that an ALA-rich diet (highest quartile 1.19 g/day) was associated with lower prevalence odds of carotid plaques and with thinner segment-specific carotid intimal/media thickness. Seidelin et al (53) also reported that patients with cerebral infarction had lower levels of ALA in subcutaneous adipose tissue than matched controls. In a case-control study (54) of 96 middle-aged men with incident stroke, Simon et al (54)

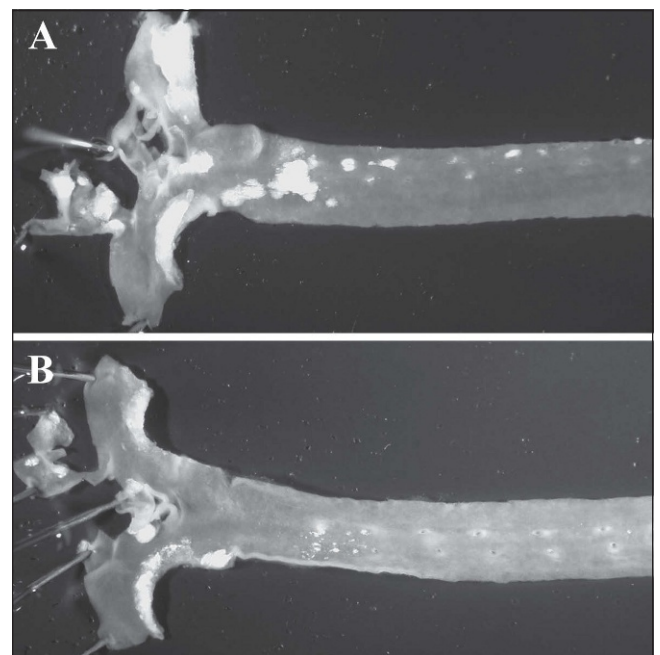


Figure 2) Atherosclerotic plaque formation in representative aortas taken from low-density lipoprotein receptor-deficient mice fed for 24 weeks with a diet supplemented with 2% cholesterol (A) or a diet supplemented with 2% cholesterol and 10% flaxseed (B). Note the significantly reduced plaque formation when flaxseed is included in the diet. Data from reference 39

found that a significant 0.06% increase in phospholipid ALA content was associated with a 28% decrease in the risk of stroke. Only ALA found in the cholesterol ester fraction was associated with a decreased risk of stroke in multivariate models. A 0.13% increase in the serum level of ALA was associated with a 37% decrease in the risk of stroke. PUFAs (particularly ALA and DHA) may be potent protectors against cerebral ischemia (55,56), possibly via the activation of the TREK-1 potassium channel (57).

Unfortunately, trials that test the beneficial effects of flaxseed in primary or secondary prevention of stroke in humans have not been conducted. Based on the data provided above, we argue that this is now warranted.

EFFECTS OF FLAXSEED AND ALA INGESTION ON SECONDARY CARDIOVASCULAR END POINTS AND CARDIOVASCULAR RISK FACTORS

The discussion above demonstrates that ALA can have significant effects on primary cardiovascular end points. Flaxseed, through its high content of ALA, may have similar effects but these data are not yet available in humans. What is impressive about these results is the consistency of the positive effects and the unusually large sample size that has been used in many of these investigations. To gain further confidence about the cardiovascular effects of flaxseed and ALA, and to gain some insight into how these substances work in our bodies, many experimental studies have examined secondary end points and risk factors.

High blood cholesterol

Most studies have reported modest effects of flaxseed on blood total cholesterol (TC), LDL cholesterol or high-density-lipoprotein (HDL) cholesterol (44,58-68). Harper et al (65) found that ALA from flaxseed (3 g/day) tends to increase the concentrations of the large, less atherogenic LDL₁ and LDL₂ subfractions. The smaller diameter and more dense LDL particles have a greater proclivity for oxidation and an enhanced ability to penetrate the intima compared with the larger, less dense LDL particles. Concentrations of these LDL particles were significant, independent predictors of new CAD events in patients undergoing treatment with gemfibrozil (66). Recently, Patade et al (67) found that mild to moderate hypercholesterolemic Native American postmenopausal women who consumed flaxseed (30 g/day) for three months exhibited a reduction of TC by 7% and LDL cholesterol by 10% without changes in HDL cholesterol or TG concentrations. Zhang et al (68) also found significant reductions in TC (22%) and LDL cholesterol levels (24%) in hypercholesterolemic subjects after an eight-week dietary supplementation with 600 mg/day of secoisolariciresinol diglucoside (SDG), a lignan derived from flaxseed. These results suggest that specific subgroups of patients could obtain more beneficial hypolipemic effects from flaxseed or its components. In general, flaxseed-enriched diets have been reported to induce anywhere from 0% to 18% decreases in LDL and 0% to 11% decreases in TC (69). With only one exception that reported a 16% decrease in HDL concentrations in men (61), most studies reported no changes in HDL levels in response to dietary flaxseed (59,63,64,70,71).

TGs

The NHLBI Family Heart Study (72), which included 4440 subjects, showed that dietary ALA (highest quintile 1.24 g/day) is associated with lower plasma TG concentrations. Zhao et al (46) demonstrated an 18% decrease in blood TG levels when patients ingested 17.5 g of ALA/day over a six-week intervention study. However, the data are not consistent. An increase (59), a decrease (47,60) or no effect on circulating TG levels (44,73) have been reported in response to a flaxseed diet. The age of the subject may be a confounding factor. Younger subjects responded with a decrease in blood TG concentrations after flaxseed (6 g ALA/day) ingestion, whereas older subjects did not (23).

Lipoprotein (a)

An elevated concentration of plasma lipoprotein (a) (Lp[a]) is a risk factor for CAD, cerebrovascular disease, atherosclerosis, thrombosis and stroke (74). In a recent double-blinded, randomized, controlled clinical trial, Bloedon et al (61) demonstrated that 40 g/day of ground flaxseed reduced Lp(a) by 14% after 10 weeks of supplementation. Similarly, Arjmandi et al (70) reported that 38 g/day of whole flaxseed lowered Lp(a) by 7.4% in postmenopausal women after six weeks of treatment.

High blood pressure

In the National NHLBI Family Heart Study (75), Djoussé et al found that dietary ALA (highest quartile 1.09 g/day) was associated with a lower prevalence of hypertension and lower systolic blood pressure in

4594 subjects. Others (76,77) have confirmed that dietary ALA is associated with lower blood pressure values. ALA may lower blood pressure by acting as a precursor for eicosanoids, which can generate the production of prostaglandins and leukotrienes that may reduce vascular tone (78).

Studies on high blood pressure (HBP) using flaxseed as a source of ALA are inconclusive. Paschos et al (73) have reported that 12 weeks of dietary flaxseed supplementation (8 g/day of ALA) resulted in a significant decrease in systolic and diastolic blood pressure in dyslipidemic patients. Conversely, Stuglin and Prasad (62) found no changes in blood pressure in a shorter four-week intervention using 32.7 g/day of total flaxseed. However, their study examined healthy men and may indicate that pathological conditions are required to detect significant changes in HBP.

The mechanism for any change in blood pressure is unclear. However, shorter studies using healthy individuals, obese subjects or dyslipidemic patients may provide some insight. Administration of 8 g of ALA/day to dyslipidemic men or 20 g/day of flax oil containing ALA to obese adults with markers of insulin resistance has resulted in significant decreases in systolic, diastolic and mean arterial blood pressure (58,73). Systemic arterial compliance was also improved significantly (58). This would agree well with experimental work in which Dupasquier et al (38) found that a flaxseed-supplemented, ALA-rich diet (12.5 g of flaxseed/day; ALA comprises 70% of total fatty acids) preserved vascular relaxation from the deleterious effects that an atherogenic, high-cholesterol diet can induce. These results would suggest that ALA may directly induce beneficial vascular effects.

Tobacco smoking

Previous studies have shown that smoking could inhibit the interconversion of short-chain PUFAs (ALA, linolenic acid) to long-chain PUFAs (EPA, DHA) (79,80). The data are limited by their focus on cigarette-smoking mothers, and the link among smoking, ALA metabolism and an increased risk for CAD in a more generalized population needs further research attention.

C-reactive protein

Patients with elevated basal levels of C-reactive protein (CRP) are at an increased risk for diabetes, hypertension and cardiovascular disease (CVD) (81). CRP levels of 0.3 mg/dL or greater are associated with a higher risk of death in patients with acute coronary syndromes (82). The intake of an ALA-rich diet (6.5% of energy/day from ALA) has been associated with a large 75% decrease in CRP levels in blood samples from hypercholesterolemic men and women (46). The authors suggested that the inhibition of vascular inflammation may result in a decrease in CVD risk. In another independent study, ALA levels in a plasma cholesterol fraction have also been negatively correlated with CRP concentrations (83). Hallund et al (84) found that SDG isolated from flaxseed (500 mg/day) reduced CRP concentration by approximately 15% in healthy postmenopausal women when they were compared with a placebo group during a six-week intervention period. These results, however, contrast with those of Dodin et al (85), who reported no changes in CRP in a similar population after 12 months of daily supplementation with 40 g of flaxseed.

Effects in obese subjects

Because of its high fat content, it is possible that flaxseed supplementation will induce weight gain. However, dietary flaxseed intervention studies (86,87) have not found any evidence of weight gain or changes in body mass index after supplementation. On the contrary, Nestel et al (58) reported that in obese human subjects, 20 g/day of ALA from flaxseed oil significantly increased arterial compliance and decreased LDL oxidation when it was compared with an oleic acid and saturated fat intervention. ALA was thought to be the component within flaxseed oil that was responsible for this effect. In overweight adolescents, a significant association among plasma fatty acid composition, metabolic syndrome and low-grade inflammation has been

identified (83). In this study, ALA levels in plasma cholesterol esters were also inversely related to CRP. From these findings, it was suggested that a high intake of long-chain PUFAs, especially ω -3 PUFAs, may protect obese subjects against metabolic syndrome and low-grade inflammation in early adolescence. Consistent with this hypothesis, Faintuch et al (87) found that morbidly obese patients decreased their white blood cell count, CRP levels, serum amyloid A and fibrinectin after two weeks of 5 g/day ALA supplementation from flaxseed. Conversely, however, Nelson et al (86) did not find an alteration in inflammatory markers after an eight-week intervention with ALA in healthy, abdominally obese adults.

In experimental animal trials, SDG significantly reduced high-fat diet-induced visceral and liver fat accumulation, hyperlipidemia, hypercholesterolemia, hyperinsulinemia and hyperleptinemia (88). The mechanism proposed for these actions was the regulation of adipogenesis-related gene expression through an increase in peroxisome proliferator-activated receptor- γ -mediated DNA binding activity induced by flaxseed lignans. Studies on differences in the conversion of ALA to EPA and DHA in obese or metabolic syndrome subjects have not been conducted.

Diabetes mellitus

Djoussé et al (89) studied 3993 nondiabetic subjects and found that a higher consumption of ALA was associated with higher plasma insulin, but not glucose levels. The authors suggested that plant-based ω -3 fatty acids might influence insulin secretion *in vivo*, and improve glucose use and efficiency. Studies in animal models of diabetes mellitus have shown that SDG from flaxseed can prevent the development of type 1 diabetes by approximately 71% (90) and type 2 diabetes by 80% (91). Pan et al (92) reported more modest but statistically significant improvements in glycemic control in type 2 diabetic patients treated for 12 weeks with 360 mg/day of flaxseed-derived lignan supplement. Das (93) has proposed that a defect in the activity of delta-6 and delta-5 desaturases (Figure 1) may be a factor that predisposes individuals to the development of insulin resistance syndrome because long-chain PUFAs can increase cell membrane fluidity, enhance the number of insulin receptors and the affinity of insulin to its receptors; suppress TNF- α , IL-6, macrophage migration inhibitory factor and leptin synthesis; increase the number of glucose transporter type 4 receptors; serve as endogenous ligands of peroxisome proliferator-activated receptors; modify lipolysis; and regulate the balance between pro- and antioxidants.

Ingestion of flaxseed or ALA may help in preventing or treating a variety of diabetic complications. For example, in 1062 adults older than 40 years of age with self-reported diagnosed diabetes, Tao et al (94) found that dietary intake of ALA (highest quintile greater than 2.11 g/day) was positively associated with lower odds of peripheral neuropathy. In an animal model, Velasquez et al (95) reported that flaxseed meals reduced proteinuria and ameliorated nephropathy in type 2 diabetes mellitus. In type 2 diabetic patients, 5 g/day of flaxseed oil consumption has been associated with a significant reduction of plasmin alpha-2-plasmin inhibitor complex level, plasminogen activator inhibitor-1 activity and thrombin antithrombin III complex level after two weeks of intervention (96). Because diabetic patients are more likely to develop thrombotic events, these findings have important clinical implications.

Coagulation and coagulation factors

Despite these findings in diabetic patients, flaxseed ingestion does not influence platelet function in healthy individuals. One might expect flaxseed and its content of ALA to induce an inhibition of platelet aggregation because fish oils (and EPA and DHA) are well-known inhibitors of platelet aggregation. However, many studies have not detected any changes in platelet aggregation after supplementing the diet with flaxseed for one to three months (20,97,98). Freese and Mutanen (99) reported no differences in collagen-induced platelet aggregation and thromboxane production,

aggregation to the thromboxane A₂ mimic I-BOP, urinary excretion of 11-dehydrothromboxane B₂ and beta-thromboglobulin, bleeding time, plasma fibrinogen concentration, antithrombin III activity, factor VII coagulant activity, or activity of plasminogen activator inhibitor 1 in healthy subjects receiving 5.9 g/day of ALA from flaxseed oil or 5.2 g/day of EPA plus DHA supplementation for four weeks. In both groups, LA intake was kept constant. In a long-term trial (six months), no differences in factors VIIa, VIIC, VIIag, XIIa, XIIag, fibrinogen concentrations, plasminogen activator inhibitor-1 or tissue plasminogen activator activity were found when subjects supplemented with PUFA of plant or marine origin were compared with the control group (98). The ratio of ω -3 PUFAs to ω -6 PUFAs in dietary fat seems to play a major role in modulating hemostatic function (100). Only two studies have shown some changes in platelet aggregation as a function of flaxseed ingestion (101); in one of these, the changes were isolated and modest at best (23). More extensive dose-response studies are needed to assess the association between ALA and any changes in bleeding times before definitive conclusions can be drawn (102).

Estrogen

Flaxseed is a rich source of lignans. Lignans are phytoestrogens that have been shown to exert hormonal effects (103). Studies conducted in postmenopausal women have reported that flaxseed supplementation (38 g/day of whole flaxseed) can lower serum LDL cholesterol, Lp(a) (70), serum TC, non-HDL cholesterol, TGs, apolipoprotein A₁ and apolipoprotein B (71). Dietary flaxseed (40 g/day of crushed flaxseed) has effects that are similar to hormone replacement therapy for decreasing menopausal symptoms (63) as well as 'hot flashes' in postmenopausal women not taking estrogen therapy (104). Recently, data collected from 56,007 French women followed over eight years showed that breast cancer risk was not related to any dietary PUFA overall and was inversely associated with ALA intake from fruit and vegetables but positively related to ALA intake from nut mixes and processed food (16). More research in this area is warranted because recent results showed that conjugated equine estrogens provided no overall protection against myocardial infarction or coronary death in generally healthy postmenopausal women during a seven-year period of use (105) and that the increased risk of breast cancer associated with the use of estrogen plus progestin markedly declined soon after discontinuation of combined hormone therapy (106).

Stress

Psychosocial factors can contribute to CAD (107). Serum ω -3 fatty acids have been associated with variations in mood, personality and behaviour in hypercholesterolemic subjects (108). Spence et al (109) reported that the rise in blood pressure during mental stress, a strong predictor of atherosclerosis progression, is ameliorated by flaxseed. The study also found a decrease in plasma cortisol values in the group treated with flaxseed. This study was conducted in high-risk postmenopausal women.

WHAT WE DO NOT KNOW ABOUT THE EFFECTS OF FLAXSEED AND ALA INGESTION ON CVD

It is important to identify not only what we currently know about dietary flaxseed and ALA but also what is not known. Secondary prevention trials using flaxseed as a source of ALA have not been conducted. No studies have been conducted on the effects of ALA or flaxseed on left ventricular hypertrophy. This could be important because ALA supplementation can reduce HBP, a state that can lead to left ventricular hypertrophy. The influence of ALA supplementation on ventricular remodelling after myocardial infarction is also unknown. There are no epidemiological or clinical randomized studies using flaxseed as a preventive intervention in a healthy population or in subjects without heart disease but who are identified as at risk for CVD disease. Because of the effects of ALA on the coronary risk

factors described above, it is logical to predict that a rich source of ALA like flaxseed should have strong beneficial effects in the primary and secondary prevention of CVD. However, without data to test this hypothesis, it remains speculative.

CONCLUSIONS

In view of these data, it is possible to advocate a potential pleiotropic effect of ALA beyond the more conventional cholesterol-lowering actions of most cardiovascular drugs. Most importantly, the body of ALA research now argues persuasively for the initiation of careful, randomized, controlled trials of dietary flaxseed and/or ALA in a patient population with symptoms of atherosclerotic heart disease.

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