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Review Article

Influence of specific nutrients on progression of atherosclerosis, vascular function, haemostasis and inflammation in coronary heart disease patients: a systematic review

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Epidemiological evidence suggests that the diet influences CHD risk, although the protective effects of dietary intervention for patients in diseased states has gained less attention. Secondary care prevention strategies for patients often involves drug therapy that is expensive and can result in undesirable side effects. Therefore, it is potentially beneficial to utilise other strategies, such as diet, in the management of CHD. A systematic review was conducted to examine the effects of specific nutrients on progression of atherosclerosis, vascular function, haemostasis and inflammation in CHD patients. Results show substantial evidence for the efficacy of *n*-3 oils in reducing cardiovascular mortality and one mechanism may be related to the stabilisation of vulnerable atherosclerotic plaques, although the effects on progression of atherosclerosis, haemostatic activity and vascular inflammation remain equivocal. Promising data also exist for the efficacy of flavonoid-rich foods for improving endothelial function, although strong clinical endpoint evidence is lacking. The variation in the efficacy of certain nutrients in CHD patients may be explained by genetics, existing risk factors, psychosocial factors and methodological issues, although these are often not adequately taken into consideration. We conclude that there is a need to undertake more appropriately designed trials in specific clinical populations, controlling for additional lifestyle and risk factors, examining potential interactions with medications, and also establishing methods to increase compliance to dietary recommendations before specific nutrients can be widely prescribed for secondary prevention. Future research should also utilise techniques that provide a direct measure of atherosclerosis.

Coronary heart disease management: Fish oils: Flavonoids: Endothelial function: Inflammation

It is well accepted that lifestyle factors, particularly diet, account for a substantial proportion of the variation in CHD risk. Thus, there is a growing worldwide interest in the prospect that food and food products can promote and maintain good health. In the past, health-focused dietary approaches have included reducing the level of salt, refined sugar and saturated fats in the diet. However, in recent years more attention has focused on promoting the consumption of specific nutrients that are present in natural food sources, which is the topic of the present review. This approach has gained support because the public in general appears to be more likely to consume nutritious food, rather than restrict themselves from something they like. In particular, the beneficial effects of dietary nutrients on cardiovascular health have been extensively explored and continue to receive considerable attention in the scientific literature. The flavonoids, which are present in high amounts in apples, onions, red wine, cocoa, red fruits, citrus fruits and tea, have undoubtedly received the most attention in relation to cardiovascular risk and data from numerous epidemiological studies generally show that a higher flavonoid intake is associated with lower CVD risk (for reviews, see Vita, 2003, 2005). Dietary sources rich in *n*-3 fatty acids, such as fish (containing EPA and DHA) and certain nuts and plants (containing α-linolenic acid), have also gained considerable attention with recent backing from the US Food and Drug Administration that has approved a heart health claim for *n*-3 fatty acids in foods and supplements. This claim is based on extensive evidence documenting the cardiovascular health benefits of *n*-3 fatty acid intake. For example, in a recent meta-analysis of fourteen cohort and five case–control-led studies, fish consumption *v.* no or little fish consumption was associated with a 20 % reduction in the relative risk of fatal and a 10 % reduction in non-fatal CHD (Whelton *et al.* 2004). Also, much attention has focused on the cardioprotective effects of the Mediterranean diet, which is characterised by a high content of

Abbreviations: AMI, acute myocardial infarction; CRP, C-reactive protein; FMD, flow-mediated dilatation; RCT, randomised controlled trial; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1.

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α-linolenic acid, phytochemicals and antioxidants (Robertson & Smaha, 2001). This interest has largely stemmed from the results of the Seven Countries Study that showed the mortality rate from CHD was two- to threefold lower in Southern Europe than in Northern Europe and America (Renaud *et al.* 1995), which was associated with the Mediterranean diet. Further prospective data have demonstrated cardiovascular health benefits for fruit and vegetable consumption (Joshipura *et al.* 2001; Liu *et al.* 2001).

In contrast, the cardiovascular health benefits of specific nutrients for CHD patients have gained less attention. In CHD patients the secondary prevention care strategies often involve drug therapy that is expensive and often results in undesirable side effects. Therefore, it is potentially beneficial to utilise other strategies, such as diet therapy, in the management of various CVD states. Given the complex physiology of CHD patients, it is important to test the efficacy of dietary interventions in patient populations and not draw on conclusions from studies with otherwise healthy participants. We therefore performed a systematic search in the MEDLINE database for literature that has examined the effect of specific nutrients on mortality, progression of atherosclerosis, vascular function, haemostasis, and inflammation in patients with established CHD. All relevant English-language articles published between 1980 and 2005 in the MEDLINE database were searched using the MeSH search terms 'coronary disease', 'inflammation', 'haemostasis', 'cardiovascular system', with the terms 'diet therapy', 'flavonoids', 'tea', 'alcohol' or 'fish oils'. The search was further limited to randomised controlled trials (RCT) and prospective cohort studies. Using these search terms a total of 325 papers were retrieved. After review of the retrieved papers for studies containing patients with established CHD, fifty-two papers were included in the present review (Table 1). The effects of vitamins and L-arginine on risk markers in CHD have been previously reviewed (Hornig, 2002; Preli *et al.* 2002; Doshi *et al.* 2003; Moat *et al.* 2004) and therefore only recent clinical outcome trials were included in the present review. Also, given that the aim of present review was to focus on the consumption of specific nutrients, interventions that involved dietary restriction (i.e. reducing energy intake, saturated fats, salt and sugar) were also excluded.

Effects of diet on risk of mortality in coronary patients

A prospective cohort study in the USA showed that self-reported moderate and heavy tea consumption in the year before acute myocardial infarction (AMI) was associated with lower mortality after infarction (Mukamal *et al.* 2002). In a prospective cohort study that examined nearly half a million US adults, and recorded deaths occurring in the subsequent 9 years, there was an L-shaped association between alcohol consumption and mortality from CHD in participants with pre-existing CVD (Thun *et al.* 1997). Thus non-drinkers recorded the greatest risk. Several studies have also shown that self-reported low to moderate alcohol consumption is associated with reduced mortality and risk of cardiovascular complications following AMI (Muntwyler *et al.* 1998; Mukamal *et al.* 2001; de Lorgeril *et al.* 2002) and in patients with left ventricular dysfunction (Cooper *et al.* 2000). However, other studies have shown alcohol intake at baseline or following AMI did not alter the risk for the development of symptomatic heart failure (Aguilar *et al.* 2004) and compared with occasional drinking, regular light alcohol consumption in men with established CHD was not associated with any benefit or deleterious effects (Shaper & Wannamethee, 2000). Collectively, these studies tend to suggest that the constituents of alcohol and tea may be associated with increased survival of patients, although given that most studies examined dietary intake before myocardial infarction, it is difficult to assess whether changes in intake following myocardial infarction had any significant impact. A further methodological issue relates to the fact that most studies measure average consumption and not drinking patterns; thus, in the case of alcohol, binge drinking may not be protective (Bobak & Marmot, 2005). Indeed, binge drinking among AMI patients has recently been associated with a two fold higher mortality rate (Mukamal *et al.* 2005). Furthermore, dietary intake may be significantly

Table 1. Studies identified in the systematic review

Reference
Aguilar *et al.* (2004)
Angerer *et al.* (2002)
Barzi *et al.* (2003)
Berstad *et al.* (2003)
Bucher *et al.* (2002)*
Burr *et al.* (1989)
Burr *et al.* (2003)
Chou *et al.* (2001)
Cooper *et al.* (2000)
de Lorgeril *et al.* (1999)
de Lorgeril *et al.* (2002)
Duffy *et al.* (2001*a*)
Duffy *et al.* (2001*b*)
Eritsland *et al.* (1995)
Erkkila *et al.* (2004)
GISSI-Prevenzione Investigators (1999)
Grundt *et al.* (2003)
Heart Protection Study Collaborative Group (2002)
Heiss *et al.* (2003)
Hodgson *et al.* (2005)
Johansen *et al.* (1999)
Kalin *et al.* (2002)
Karatzi *et al.* (2004)
Karatzi *et al.* (2005)
Kothny *et al.* (1998)
Liem *et al.* (2003)
Lonn *et al.* (2005)
Mukamal *et al.* (2001)
Mukamal *et al.* (2002)
Mukamal *et al.* (2005)
Muntwyler *et al.* (1998)
Rapola *et al.* (1997)
Sacks *et al.* (1995)
Seierstad *et al.* (2005)
Seljeflot *et al.* (1999)
Shaper & Wannamethee (2000)
Stein *et al.* (1999)
Stephens *et al.* (1996)
Thies *et al.* (2003)
Thun *et al.* (1997)
Toole *et al.* (2004)
von Schacky *et al.* (1999)
Waters *et al.* (2002)
Whelan *et al.* (2004)
Widlansky *et al.* (2005)
Williams *et al.* (2004)

* Includes six additional studies.

confounded by socio-economic status; for example Nielsen *et al.* (2004) have suggested that the relationship between wine intake and mortality is confounded by the fact that wine is predominantly consumed in groups of higher socio-economic status. Thus some or all of the apparent protective effects of moderate alcohol consumption may be due to residual or unmeasured confounding, and definitive RCT are required to confirm the effects on clinical endpoints in CHD patients.

Supplementation with *n*-3 fish oils has gained substantial interest, and the American Heart Association recommends that patients with documented CHD should consume up to 1 g *n*-3 fish oil per d (Kris-Etherton *et al.* 2002). These recommendations have largely evolved from several large-scale RCT that demonstrate treatment with *n*-3 fish oils following AMI is associated with a reduction in all-cause and cardiovascular death (Burr *et al.* 1989; GISSI-Prevenzione investigators, 1999). Furthermore, in a recent meta-analysis of eleven RCT in CHD patients, intake of *n*-3 fatty acids was shown to significantly reduce overall mortality, mortality due to myocardial infarction, and sudden death (Bucher *et al.* 2002). (In that meta-analysis, work by Singh and colleagues in relation to *n*-3 fish oils was excluded (see White, 2005).)

Several studies have also examined the efficacy of the Mediterranean diet in the secondary prevention of CHD. For example, in the Lyon Diet Heart study, de Lorgeril *et al.* (1999) demonstrated that a Mediterranean diet substantially reduced the recurrence of CHD events for up to 4 years after AMI compared with a low-fat-diet, which was independent of traditional risk factors such as high cholesterol and hypertension. Similarly, in the GISSI-Prevenzione study, patients who successfully adopted the Mediterranean diet after AMI demonstrated lower risk of all-cause mortality over a 6·5-year follow-up period (Barzi *et al.* 2003). These findings strongly support the efficacy of the Mediterranean diet as a secondary prevention care strategy, although it is difficult to determine which individual components of the diet account for these effects. Paradoxically, it has been suggested that a high intake of the 18-carbon α-linolenic acid, a key component of the Mediterranean diet, is often accompanied by increases in haemostatic markers that are risk factors for CHD (Miller, 2005). However, these haemostatic risk factors may be of little consequence if the arterial wall is healthy and in combination with a high intake of phytochemicals and antioxidants provided by the diet.

One of the Bradford Hill criteria for accepting an association between exposure and disease outcome as causal is the existence of a biological mechanism (Hill, 1965). Some of the proposed mechanisms by which these specific nutrients may confer benefits for disease management include attenuation of inflammatory processes, reducing thrombosis, and improving endothelial function. These mechanisms have been specifically investigated using short-term intervention studies that will now be reviewed.

Mechanisms of action

Vascular function, haemostasis and inflammation

Atherosclerosis, which is the disorder underlying CHD, is largely viewed as an inflammatory process in which leucocytes interact with structurally intact but dysfunctional endothelium of the arteries (Ross, 1999; Libby, 2002). Inflammatory markers such as C-reactive protein (CRP) and IL-6 may directly influence plaque vulnerability and rupture (Blake & Ridker, 2001). The vascular endothelium also plays a key role because endothelium-derived NO has important vasodilator, anti-inflammatory, anti-thrombotic and growth-suppressing properties that are relevant to all stages of atherosclerosis (Vita & Keaney, 2002). Soluble forms of cellular adhesion molecules, such as intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1), are considered to be markers of endothelial activation (Frijns *et al.* 1997) and are elevated in patients suffering from CHD and AMI, and also appear to be a prognostic factor in AMI (Zeitler *et al.* 1997). Recent research has focused on these mechanisms in relation to the efficacy of specific nutrients for the secondary prevention of CHD (see Fig. 1).

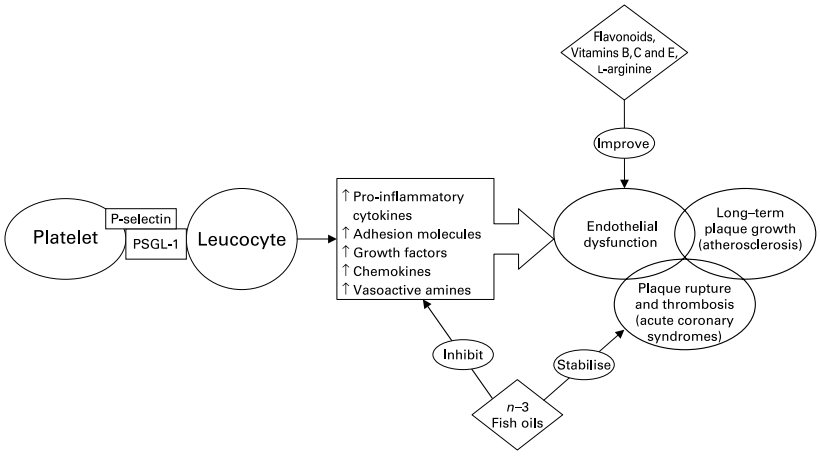

Fig. 1. Proposed mechanisms of specific nutrients in relation to the progression of atherosclerosis. Platelet activation results in platelet surface expression of the adhesion molecule P-selectin which binds to the leucocyte receptor, P-selectin glycoprotein ligand-1 (PSGL-1), leading to the formation of platelet–leucocyte aggregates. These interactions result in the release of a number of adhesive and pro-inflammatory molecules which stimulate a variety of processes promoting long-term CHD. Specific nutrients may potentially intervene with some of these processes.

Flavonoid-rich dietary components

A substantial number of intervention studies have been conducted to examine the effects of flavonoid-rich beverages on vascular function, haemostasis, and inflammation in CHD patients (summarised in Table 2). Improvements in endothelial-dependent dilatation (measured by flow-mediated dilatation; FMD) have been consistently observed in RCT after both acute and chronic intake of green and black tea (Duffy *et al.* 2001*a*; Hodgson *et al.* 2005; Widlansky *et al.* 2005). These findings are corroborated by recent *in vitro* work using endothelial cells that has demonstrated the polyphenolic fractions found in green and black tea acutely enhance NO bioavailability (Anter *et al.* 2004; Lorenz *et al.* 2004). The mechanism may be linked with the antioxidant effects of these polyphenolic fractions because it has been demonstrated that NO activity may be impaired by free radical production, but is improved during infusion of vitamin C (Levine *et al.* 1996; Solzbach *et al.* 1997; Taddei *et al.* 1998; Lembo *et al.* 2000). However, there are often no improvements in antioxidant status after tea intake, which therefore does not support an antioxidant mechanism. Furthermore, Widlansky *et al.* (2005) recently showed that the improvement in endothelial function following a 4-week tea intervention was not correlated with changes in catechin level, although baseline endothelial function was correlated with dietary flavonoid intake. Thus the authors suggested that the effects may be due to non-catechin components of tea such as polymeric polyphenols or other mechanisms such as tea components acting to chelate transition metals or alter the absorption of other dietary components such as oxidised lipids.

Red wine has gained much attention in relation to its cardioprotective effects, although the findings regarding vascular function are somewhat unclear. Recent studies in CHD patients have shown that acute ingestion of red wine both improves (Whelan *et al.* 2004) and has no effects on FMD (Karatzi *et al.* 2004). De-alcoholised wine has also been shown to have beneficial acute effects on FMD, arterial stiffness, and blood pressure in CHD patients, suggesting that the effects are due to the constituents of the wine and not the alcohol (Karatzi *et al.* 2004, 2005), although this remains a contentious issue in the epidemiological literature (Bobak & Marmot, 2005). Furthermore, the acute effects of wine ingestion on FMD may be confounded by the vasodilatory effects of alcohol (Agewall *et al.* 2000), and chronic intervention studies in CHD patients are therefore required to clarify the benefits of red wine. Several other studies in CHD patients using grape juices that have employed chronic intervention designs (Stein *et al.* 1999; Chou *et al.* 2001) have shown favourable effects on endothelial function, although both trials were not placebo controlled. There is also evidence from one study to show that plasma levels of sVCAM-1, sICAM-1, and P-selectin were reduced in systemic sclerosis patients after administration of proanthocyanidins (100 g/d for 1 month) derived from grape seeds (Kalin *et al.* 2002). A further study in patients with at least one CVD risk factor, including history of CHD, hypertension, or hyperlipidaemia, demonstrated increased plasma NO bioactivity and improved FMD following a single dose of a cocoa drink rich in flavan-3-ols (Heiss *et al.* 2003).

In contrast to the effects on endothelial function there is no evidence from studies in CHD patients to support an effect of tea intake on inflammation (Widlansky *et al.* 2005) or platelet aggregation (Duffy *et al.* 2001*b*). Similarly, there do not appear to be any effects of red wine on inflammatory markers or fibrinogen in CHD patients after acute intake (Karatzi *et al.* 2004; Williams *et al.* 2004). One possible reason for null findings in relation to procoagulant activity may relate to methodological issues. For example, previous measures of platelet activation have involved using the platelet aggregometer device, and plasma concentrations of various platelet secretory products such as soluble P-selectin and β-thromboglobulin. However, these techniques involve a relatively large amount of sample manipulation before analysis and display large variability among individuals, which limits their utility. More recent methods using flow cytometry are thought to provide a more accurate assessment of platelet activity (Michelson *et al.* 2001) and future studies using this method may therefore produce more reliable results.

n-*3 Fish oils*

A number of larger studies with longer intervention periods have examined the effects of *n*-3 fish oils on progression of atherosclerosis, vascular function and inflammation, and atherosclerotic plaque stability. Fish oil supplementation for 2 years in an RCT had no effect on the progression of atherosclerosis, as assessed by changes in carotid artery wall thickness using ultrasound (Angerer *et al.* 2002) and was both effective (von Schacky *et al.* 1999) and ineffective (Sacks *et al.* 1995) in reducing progression using angiography to measure coronary lumen narrowing. Also, in a prospective cohort study, consumption of at least two servings of fish per week compared with lower intakes was associated with reduced progression of atherosclerosis at 3 years follow-up, as assessed by angiography, in postmenopausal women with CHD and diabetes (Erkkila *et al.* 2004). In addition, the effects of fish oil on the prevention of post-angioplasty restenosis appear to be equally unclear (for a review, see de Lorgeril & Salen, 2003). However, given that these measures provide little information about plaque inflammation or risk of plaque rupture (Hong *et al.* 1994; Davies *et al.* 2004), they do not directly measure atherosclerosis and are therefore not definitive studies.

Baumann *et al.* (1999) have demonstrated reductions in human gene expression of platelet-derived growth factor and monocyte chemoattractant protein after 4 weeks of fish oil supplementation, both of which are important modulators of the inflammatory response associated with the progression of atherosclerosis. However, the effects of fish oil on other inflammatory and haemostatic markers is less clear (see Table 2). In patients recovering from AMI, studies have shown rather surprising increases or no changes in vascular inflammatory markers such as E-selectin and sVCAM-1 (Johansen *et al.* 1999; Grundt *et al.* 2003) following fish oil supplementation, although more favourable effects on haemostatic activity (Johansen *et al.* 1999), homocysteine, triacylglycerols, and HDL-cholesterol (Grundt *et al.* 2003). Elderly men with high risk for CHD that were supplemented with fish oils for 18 months also demonstrated a positive correlation between serum non-esterified DHA and sVCAM-1 (Berstad

Table 2. The effects of specific nutritional intervention on vascular function, haemostasis and inflammation in coronary patients

Study and food	Intervention, dietary restriction and design	Participants	Evidence of compliance or nutrient uptake	Findings	Comments
Tea					
Widlansky *et al.* (2005)	Black tea or hot water (900 ml/d) for 4 weeks. Also acute effects (2 h) after 450 ml tea or water DR: tea and red wine. RCT, C/O, SB	Sixty-six CHD patients (mean age 54 years)	↑ Plasma catechins	↑ FMD (56·7 and 58·3 %) for acute and chronic tea intake compared with baseline. No effects on CRP	No changes in AOX status or oxidative stress. Improvements in FMD not correlated with ↑ catechins
Hodgson *et al.* (2005)	Black tea or water (250 ml) after high-fat meal or no meal. DR: wine, suppl, limited tea and coffee intake. RCT, treatments 1 week apart	Twenty CHD patients (45–70 years)	↑ Urinary excretion of 4OMGA	↑ FMD after meal + tea compared with meal + water; ↑ FMD after tea compared with water (after adjusting for change in plasma caffeine). ↑ FMD after meal + tea (20·4 %) compared with baseline	Relatively small size with no control measures for diurnal variation in FMD
Duffy *et al.* (2001*a*)	Black tea or hot water (900 ml/d) for 4 weeks. Also acute effects (2 h) after 450 ml tea or water DR: tea and red wine. RCT, C/O, SB	Fifty CHD patients (mean age 55 years)	↑ Plasma catechins	↑ FMD (56·7 and 58·3 %) for acute and chronic tea intake compared with baseline	No change in oxidative stress measures
Duffy *et al.* (2001*b*)	Black tea or hot water 900 ml/d) for 4 weeks. Also acute effects (2 h) after 450 ml tea. DR: tea and red wine. RCT, C/O, SB	Forty-nine CHD patients (mean age 55·1 years)	↑ Plasma catechins	No effects of tea on platelet aggregates or LDL-cholesterol	Reliability of platelet results from using an aggregometer device is questionable
Red wine					
Whelan *et al.* (2004)	Acute effects 1 and 6 h after red or white wine (4 ml/kg), or cordial drink (with light meal). DR: alcohol, AOX suppl. RCT, C/O, SB	Fourteen CHD patients (mean age 58 years)	↑ Blood alcohol	↑ FMD (180 and 88 %) for white and red wine compared with baseline (6 h post-consumption)	Low sample size, no control for diurnal variation
Karatzi *et al.* (2005)	Acute effects 30, 60, 90 min after 250 ml regular or de-alcoholised red wine (with light meal). RCT, C/O, DB	Fifteen CHD patients (mean age 52·4 years)	None	↓ PWV (10·5 and 6·1 %) for regular and de-alcoholised wine, respectively; ↓ central BP after both beverages	Low sample size
Karatzi *et al.* (2004)	Acute effects 30, 60, 90 min after 250 ml regular or de-alcoholised red wine (with light meal). RCT, C/O, DB	Fifteen CHD patients (mean age 52·4 years)	None	↑ FMD (110 %) for de-alcoholised wine, ↓ FMD (26 %) for regular wine compared with baseline (30 min post-consumption)	Low sample size, no control for diurnal variation
Williams *et al.* (2004)	Acute effects 1 and 6 h after red or white wine (4 ml/kg), or cordial drink (with light meal). DR: alcohol, AOX suppl. RCT, C/O, SB	Thirteen CHD patients (mean age 59 years)	↑ Blood alcohol	↑ IL-6 for red and white wine intake compared with baseline (6 h post-consumption). No effects on sICAM-1 or sVCAM-1	Low sample size
Grape extract					
Stein *et al.* (1999)	Purple grape juice (7·7 ml/kg per d) for 14 d. DR: fruit products, tea, alcohol. NPC	Fifteen CHD patients (mean age 62·5 years)	None	↑ FMD (190 %) post-intervention compared with baseline. ↑ HDL cholesterol, ↓ LDL oxidation	No control condition and very low sample size weaken strength of findings
Chou *et al.* (2001)	Purple grape juice (4 or 8 ml/kg per d) for 4 weeks. DR: vitamin suppl, fruit products, tea, alcohol. NPC	Twenty-two CHD patients (mean age 64 years)	None	↑ FMD (190 %) post-intervention compared with baseline (not dose-dependent)	No control condition and low sample size
Kalin *et al.* (2002)	Activin (100 mg/kg) for 30 d. DR: AOX suppl. RCT, DB	202 Systemic sclerosis patients	↓ Oxidative stress	Significant ↓ in vascular adhesion markers (sICAM-1, sVCAM-1, E-sel), except P-sel	A comprehensive and well-controlled study

Table 2. *Continued*

Study and food	Intervention, dietary restriction and design	Participants	Evidence of compliance or nutrient uptake	Findings	Comments
Cocoa					
Heiss *et al.* (2003)	Acute effects 2 h after 100 ml cocoa drink (with high, 176 mg, or low, <10 mg, flavan-3-ol). RCT, C/O, DB	Twenty out-patients with CV risk factors (mean age 41 years)	None	↑ FMD (85 %) for high active cocoa drink only compared with baseline. ↑ Plasma nitrosated compounds	Significant strength of study is use of DB design
n-3 Fish oils					
Eritsland *et al.* (1995)	*n*-3 Fatty acids (3·4 g/d) for 6 months. RCT	Thirty-two CHD patients	None	No effects on LPS-stimulated monocyte pro-coagulant activity and IL-6	–
Kothny *et al.* (1998)	Acute effects of 18 g *n*-3 fatty acids in 24 h or fatty acid placebo (none *n*-3). RCT, DB	Eighteen CHD patients (47–64 years)	None	No effects on FMD and GTN responses	Very high dosage
Seljeflot *et al.* (1999)	*n*-3 Fatty acids (5·1 g/d) or maize oil placebo for 6 months. RCT	Twenty-three CHD patients	Serum fatty acids	↓ LPS-induced prothrombin fragment but ↑ IL-6, TNF-α in *n*-3 group	Relatively small, only eleven patients received intervention
Johansen *et al.* (1999)	*n*-3 Fatty acids (5·1 g/d) or maize oil placebo for 6 months. RCT	Fifty-four CHD patients (mean age 57·5 years)	Serum fatty acids	↓ vWF, s-TM; ↑ E-sel, sVCAM-1 in *n*-3 group. No effects on P-sel or t-PA	–
Berstad *et al.* (2003)	*n*-3 Fatty acids (2·4 g/d) or maize oil placebo for 18 months. RCT	171 Men with high risk of CHD (mean age 70 years)	Serum fatty acids	Positive correlation between change in *n*-3 fatty acids and sVCAM-1. No effects on sICAM-1, P- and E- sel, t-PA, s-TM	Elderly sample may have impacted upon findings
Grundt *et al.* (2003)	*n*-3 Fatty acids (3·5 g/d) or maize oil placebo for 1 year. RCT	300 acute MI patients	Capsule counts, serum fatty acids	↓ p-tHcy and ↑ HDL-cholesterol in *n*-3 group. No effects on sICAM, E-sel, CRP	A comprehensive and well controlled study
Seierstad *et al.* (2005)	700 g/week, 6 weeks Atlantic salmon fed with 100 % fish oil, rapeseed oil, or 50 % of each. RCT, DB	Sixty CHD patients (46–75 years)	Serum fatty acids	↓ IL-6, sVCAM-1, triacylglycerols, ↓ HDL cholesterol in group consuming fish oil-fed salmon. No effects on sICAM-1, P- and E-sel, TNF-α, IL-10, CRP	Significant strength of study is the use of a fresh fish intervention that is less likely to contain oxidation by-products. However, intervention period relatively short

DR, dietary restriction; RCT, randomised controlled trial; C/O, cross-over; SB, single blind; ↑, increase; FMD, flow-mediated dilatation (endothelium dependent); CRP, C-reactive protein; AOX, antioxidant; suppl, supplements; 4OMGA, 4-O-methylgallic acid; DB, double blind; ↓, decrease; PWV, pulse wave velocity; BP, blood pressure; NPC, non-placebo controlled; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; E-sel, E-selectin; P-sel, P-selectin; LPS, lipopolysaccharide; GTN, glyceryl trinitrate (endothelium independent); vWF, Von Willebrand factor; s-TM, soluble thrombomodulin; t-PA, tissue type plasminogen activator; MI, myocardial infarction; p-tHcy, plasma homocysteine.

et al. 2003). In clinically stable CHD patients, reductions in sVCAM-1 and IL-6 were observed (Seierstad *et al.* 2005), although no effects on lipopolysaccharide-stimulated monocyte procoagulant activity or IL-6 release (Eritsland *et al.* 1995). In contrast, Seljeflot *et al.* (1999) observed beneficial effects on procoagulant activity but adverse effects on inflammatory markers IL-6 and TNF-α after 6 months of supplementation in CHD patients. Also, short-term fish oil treatment in clinically stable CHD patients did not appear to promote favourable changes in endothelial function (Kothny *et al.* 1998). Interestingly, CRP appears to be consistently unaffected by fish oil supplementation (Grundt *et al.* 2003; Seierstad *et al.* 2005). Despite robust epidemiological data demonstrating a consistent relationship between CRP and CVD risk (Danesh *et al.* 2004), the mechanisms relating CRP to incident cardiovascular events are unclear and recent data from a large population-based sample suggest CRP is a poor predictor of atherosclerotic burden after adjustment for traditional risk factors (Khera *et al.* 2006).

The wide variation in the dosage, EPA:DHA ratios, and source (diet or supplement) of various fish oil interventions may be one explanation for the equivocal findings, although the meta-analysis by Bucher *et al.* (2002) did not identify effects of these parameters in relation to clinical outcomes. Another possible explanation relates to studies on polymorphisms of the endothelial NO synthase gene (Leeson *et al.* 2002) and the inflammatory cytokine, TNF-α gene (Grimble *et al.* 2002), which suggest only certain patients could benefit from *n*-3 fatty acid supplementation. An explanation for the negative effects of fish oil supplementation on vascular function and inflammatory markers may be related to poor-quality fish oil that contains oxidation by-products and is therefore likely to cause an increase in peroxidation that can result in increased expression of adhesion molecules via a NF-κB pathway (Collins, 1993). However, in a recent landmark study in the UK, atherosclerotic plaque stability was shown to be improved after a modest level of *n*-3 fish oil supplementation (1·4 g/d for a median of 42 (range 7–189) d) in 188 patients awaiting carotid endarterectomy surgery (Thies *et al.* 2003). In this study, *n*-3 PUFA from fish-oil were observed to be readily incorporated into atherosclerotic plaques that significantly reduced macrophage numbers within the plaque and thus reducing the vulnerability of rupturing. Given that vulnerability of the plaque to rupture is the primary determinant of acute cardiovascular events (Ross, 1999), this finding may explain the protective effects of fish oil towards fatal myocardial infarction and may render the potential vascular inflammatory effects insignificant. Recent developments in techniques, such as electron-beam computed tomography that provide direct information about coronary artery plaque, and therefore give more prognostic information on hard CHD endpoints in comparison with previous screening methods (Clouse *et al.* 2006), may also be utilised in future studies to examine the effects of fish oils on plaque progression. Indeed, recently electron-beam computed tomography was used in a study that showed an inverse relationship, in a dose–response fashion, between dietary consumption of linolenic acid and prevalence of calcified atherosclerotic plaque in the coronary arteries, after adjusting for other risk factors (Djousse *et al.* 2005).

Vitamins and L-arginine

Last, a number of previously reviewed supplements, which include vitamins C and E (Hornig, 2002), folic acid (Doshi *et al.* 2003; Moat *et al.* 2004), and L-arginine (Preli *et al.* 2002), have also demonstrated beneficial effects on various markers of vascular function in CHD patients. Nevertheless, evidence from RCT with clinical endpoints is equivocal. For example, recent prospective data from the Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that 7 years' supplementation with vitamin E (α-tocopherol; 400 IU/d) in patients with vascular disease or diabetes mellitus was not efficacious for the prevention of major cardiovascular events and was actually connected with a higher risk of heart failure (HOPE Trial Investigators; Lonn *et al.* 2005). Similar large-scale RCT in CHD patients have demonstrated benefits of vitamin E for reducing cardiovascular events (Stephens *et al.* 1996; Rapola *et al.* 1997), although others have not (GISSI-Prevenzione Investigators, 1999). Also, studies using a mixture of antioxidant supplements have shown little benefit (Heart Protection Study Collaborative Group, 2002; Waters *et al.* 2002). Furthermore, recent RCT in CHD and cerebral infarction patients have shown no effects of B vitamin supplementation on clinical endpoints (Liem *et al.* 2003; Toole *et al.* 2004), despite significant reductions in homocysteine that has been described as an independent predictor of mortality in CHD patients (Nygard *et al.* 1997). The growing literature therefore supports the hypothesis that antioxidants might be effective only over many years and therefore can only be successfully utilised for primary prevention (Steinberg, 1995). The reasons for the possible negative effects of vitamin supplementation may be linked with the supra-physiological dosages used in some trials that may exert harmful, pro-oxidant effects.

Mediating factors

Various parameters including lifestyle, health behaviours, psychological stressors, genetics, and existing risk factors may interact to determine prognosis in CHD patients. Thus, the existence of factors such as hypertension, hyperlipidaemia, obesity, smoking, medication, sedentary lifestyle, and depression may explain the variation in the efficacy of certain nutrients in CHD patients. For example, psychosocial factors are potent pathways for CHD development (Rozanski *et al.* 2005) and are also linked with an increased risk of mortality in men with CHD (Barth *et al.* 2004). Interestingly, in a case–control study Frasure-Smith *et al.* (2004) showed that depressed patients recovering from acute coronary syndromes had significantly lower serum concentrations of total *n*-3 and DHA, and higher arachidonic acid:DHA, arachidonic acid: EPA, and *n*-3:*n*-6 ratios than controls. Therefore the intriguing association between *n*-3 fish oils, depression, and cardiovascular mortality risk in CHD patients should receive more attention in order to resolve the causal pathways. Given that mental stress and emotional factors are known to act as acute triggers for coronary events (Strike & Steptoe, 2005) and CHD patients demonstrate mental stress-induced ischaemia (Strike & Steptoe, 2003), and heightened platelet activation and haemodynamic reactivity (Strike *et al.* 2004), specific nutrients that lower stress responsiveness may be particularly beneficial.

Table 3. Summary of the known effects of specific nutrients for secondary prevention

Nutrient	Clinical endpoints	CHD risk markers
n-3 oils	↓ All-cause and cardiovascular mortality; ↓ cardiac events; inconclusive effects on progression of atherosclerosis	Variable effects on inflammation and haemostatic activity; stabilisation of vulnerable atherosclerotic plaque
Flavonoids	Inconclusive	Improved FMD; limited effects on inflammatory and haemostatic markers
B vitamins and folic acid	Inconclusive	↓ Homocysteine; improved FMD
Vitamins C and E	Inconclusive	Improved FMD
L-Arginine	Inconclusive	Improved FMD

FMD, flow-mediated dilatation.

Although previous studies in healthy participants have indicated that certain nutrients, including vitamin C, *n*-3 fish oils, and α-lactalbumin may be effective in reducing psychobiological stress responses (Hamer *et al.* 2005), future studies in CHD patients are required.

Conclusion

There appear to be a number of specific nutrients that may be efficacious in the management of CHD (summarised in Table 3). Interventions that have used *n*-3 fish oils and Mediterranean-style diets have demonstrated beneficial effects on clinical endpoints, although at present the mechanisms are unclear. The potential mechanisms conferring benefits of *n*-3 oils include stabilisation of vulnerable atherosclerotic plaques, although the effects on haemostatic activity and vascular inflammation remain equivocal. Extensive clinical endpoint data in patients for the efficacy of other nutrients are lacking, although several important findings have been identified that include the effects of foods high in flavonoid content (especially tea) on endothelial function in CHD patients. Based on this evidence, various composite diets, such as the Mediterranean (Robertson & Smaha, 2001) and the Polymeal (Franco *et al.* 2004), could be potentially efficacious as secondary prevention care strategies for CHD patients.

However, there are a number of issues that should be considered. First, whether or not CHD patients are willing to comply with dietary recommendations is debatable. For example, Burr *et al.* (2003) demonstrated no benefits of dietary advice (eating more fish, fruits and vegetables) on all-cause mortality after 3–9 years' follow-up in elderly men with angina, which was probably attributable to poor compliance. Second, it is clear that the existence of other lifestyle and risk factors, genetics, existing medication, and nutritional status are not always adequately controlled for, which may explain the variation in the efficacy of certain nutrients. Last, some of the recent large-scale trials that have shown adverse effects of vitamin E and *n*-3 fish oil supplementation on clinical endpoints suggest that there may be potentially harmful interactions of some nutrients with specific disease states. Therefore taken together, there is a need to undertake more appropriately designed trials in specific clinical populations, controlling for additional lifestyle and risk factors, examining potential interactions with medications, and also establishing methods to increase compliance to dietary recommendations before specific nutrients can be widely prescribed for secondary prevention. In addition, future research should utilise techniques that provide direct measures of coronary artery plaque in order to perform a valid assessment of how nutritional interventions influence the progression of atherosclerosis.

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