Review
A review of clinical trials in dietary interventions to decrease the incidence of coronary artery disease

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Abstract

Of the associations between dietary elements and coronary artery disease (CAD), the greatest body of evidence deals with the beneficial effect of reducing the dietary intake of saturated fatty acids and cholesterol. Furthermore, it is well established, on the basis of convincing evidence, that reduction in serum total cholesterol results in reduction in coronary morbidity and mortality, as well as in regression of other atherosclerotic manifestations. In fact, dietary intervention studies revealed that it is possible to reduce the incidence of coronary death and nonfatal myocardial infarction, as well as manifestations of atherosclerosis in cerebral and peripheral arteries, by reducing dietary intake of saturated fat and cholesterol. In two recently reported dietary interventions the incidence of coronary events, especially coronary mortality, and total mortality were reduced by increased intake of n-3 long-chain polyunsaturated fatty acids and by a modification of the diet toward a Mediterranean-type diet (rich in α-linolenic acid. In addition to those findings, the potential efficacy of the dietary newcomers phytostanol and phytosterol esters on reducing coronary incidence is discussed in the present review.

Keywords cholesterol, coronary artery disease, diet, fatty acids, plant stanols, plant sterols

The literature concerning the associations between various dietary elements and coronary artery disease (CAD) extends from antioxidants to alcohol and from mice to humans, through data from large observational studies to clinical trials. The largest body of information deals with dietary cholesterol and fat. Indeed, the only evidence-based means identified thus far by which atherosclerotic lesions can be retarded or even regressed is by lowering the serum cholesterol concentration. The effects of vitamins, provitamins and/or other antioxidants on atherosclerosis are still controversial. Elevated serum homocysteine concentration, which has an unquestionable association with the risk for CAD in epidemiological studies, still lacks definitive confirmation as a causal factor in development of atherosclerosis. We must await the results of ongoing clinical trials, which will determine whether lowering homocysteine by treatment with vitamin therapy will reduce the incidence of CAD. Therefore, the present review is limited to the evidence regarding dietary fats and cholesterol, including that related to 'functional foods' that contain certain newcomers to the dietary fats – phytostanol and phytosterol esters.

Dietary fat and cholesterol
Observational studies

During the 1950s and 1960s, an indisputable relationship between diet and CAD was identified in most of the large epidemiological follow-up studies conducted [1]. The abundance of dietary total fat [2–4], especially that of saturated fatty acids [2,3,5,6] and cholesterol [3,4,7], was independently related to mortality associated with CAD. In a recent prospective cohort study in healthy women ($n = 80,082$) aged 34–59 years [8], the amount of saturated and trans-unsaturated fat intake was significantly associated with increased risk for CAD during a follow-up period of 14 years. Dietary intakes of cholesterol and total

AHA = American Heart Association; CAD = coronary artery disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

fat were not associated with the risk for CAD in that study. It was estimated that replacement of 5% of energy from saturated fat and 2% from trans-unsaturated fatty acids by unsaturated fats would reduce the CAD risk by 42 and 53%, respectively. However, in a recent prospective cohort study of healthy males ($n = 43,757$) aged 40–75 years [9], significant associations were observed between the intakes of cholesterol, saturated fat and trans-fatty acids, and risk of CAD during a 6-year follow up, but these associations were attenuated following adjustment for intake of fibre. Intake of α-linolenic acid was inversely associated with myocardial infarction after adjustment for age and standard risk factors.

The study populations in both of these studies [8,9] were health professionals (nurses and male health professionals), and it may be speculated that their dietary and living habits may not be comparable to those of the general population. Regarding fibre intake, the recent American Heart Association (AHA) Dietary Guidelines [10] recommend increasing fibre intake by increasing consumption of vegetables, cereals, grains and fruits, but that fibre supplements are not recommended for heart disease risk reduction.

Dietary interventions
It was shown by two large pioneering interventions [11,12] that it is possible to reduce the incidence of CAD by dietary means only. In those long-term controlled studies, with up to 8- and 12-year follow-up periods, two dietary variables were changed; the amount of dietary cholesterol was reduced by approximately 40%, and fat intake was modified to contain less saturated and more unsaturated fatty acids (saturated fatty acids constituted 26% of total fatty acids in the experimental versus 54% in the control diet [12]; and decrease in palmitic acid and four-fold increase in linoleic acid [11]). In accordance with recent recommendations [10] the intake of total fat was rather high (approximately 110 g/day in both studies). Serum cholesterol was reduced by 13% [11] and 15% [12]. The incidences of end-points – coronary death [12], and nonfatal and fatal myocardial infarction and manifestations of atherosclerosis in cerebral and peripheral arteries [11] – were significantly lower in the experimental groups than in the control groups.

In a third intervention study, which included 1232 healthy, 40- to 49-year-old hypercholesterolaemic men [13], coronary end-points were reduced by 47% over a 5-year period through cessation of smoking and alterations in fat intake. In that study, total fat calories were reduced to 28% in the experimental group and were 44% in the control group. The major change was in the intake of saturated fat (8% versus 18% in the intervention versus control cohort) and cholesterol (289 mg/day versus 527 mg/day), resulting in a reduction in serum cholesterol by 13% and in triglycerides by 20% in the intervention group. These classical dietary intervention studies indicate that coronary disease can be controlled by varying dietary cholesterol and total and saturated fat intake.

In these interventions, and in most of the observational prospective epidemiological studies, there was a clear-cut reduction in serum cholesterol level by more than 10%. Law et al [14] estimated that, provided serum cholesterol is reduced by 10% (0.6 mmol/l), the decrease in risk for CAD in 50-year-old individuals is approximately 39%, in those aged 60 years it is approximately 27%, and in those aged 70 years it is approximately 20%. If serum cholesterol is reduced further, then the risk reduction is more effective; this has recently been confirmed by five large statin trials [15–20], including a total study population in excess of 30,000 individuals. Reduction in serum cholesterol level by 10% is possible by reducing dietary cholesterol or saturated fat intake, and these dietary changes can be expected to result in reduction in risk for CAD. However, in many Western populations, dietary habits have already been changed such that the diet modifications described above will usually reduce serum cholesterol by 10%.

The physiological mechanisms by which dietary cholesterol and saturated fatty acids increase serum cholesterol level are well documented [21]. Abundance of dietary cholesterol expands the small regulatory hepatic intracellular pool of free cholesterol, which results in reduced LDL-receptor activity, reduced LDL-cholesterol catabolism, and increased serum total cholesterol and LDL-cholesterol levels; this has also been demonstrated in human kinetic studies [22,23]. The long-chain saturated fatty acids (C12-16:0) interfere with the esterification process of free cholesterol, and by this mechanism enlarge the hepatic regulatory free cholesterol pool [21]. Similar to in dietary cholesterol excess, LDL-receptor transcription is reduced, resulting in diminished LDL catabolism; this has also been observed in human kinetic studies [24,25]. Although it has been shown that oleic acid (C18:1) increases cholesterol esterification in hepatocytes, diminishes the free cholesterol pool and enhances LDL-receptor activity, epidemiological studies [1] have not shown any consistent effect of monounsaturated fatty acids on risk for CAD. The trans-fatty acids increase serum total cholesterol and LDL-cholesterol levels, but their importance as independent risk factors for CAD has not consistently been verified either [26]. However, in the recent AHA Dietary Guidelines [10], it is recommended that intake of trans-fatty acids be reduced because of their effect on serum cholesterol level.

n-3 Polyunsaturated fatty acids from fish oils
The numerous studies that dealt with the impact of intake of fish-based n-3 polyunsaturated fatty acids (EPA and docosahexaenoic acid [DHA]) on serum lipid levels have recently been reviewed [27]. The conclusion from those

studies was that ingestion of n-3 polyunsaturated fatty acids from fish oils decreases serum triglycerides by 25–30%, but have little effect on total cholesterol, LDL-cholesterol and high-density lipoprotein (HDL)-cholesterol levels. Their effect on the incidence of CAD, however, is more difficult to interpret. According to numerous older and two recent large prospective observational studies with lengthy follow-up periods, there is a clear [28] or no [29] association between fish oil intake and risk for CAD.

In another pioneering dietary intervention study, male patients with myocardial infarction ($n = 2033$) were advised to change their dietary habits for 2 years [30]. One group was advised to reduce fat intake to 30% of total calories, and to reduce the intake of saturated fatty acids and increase that of polyunsaturated fatty acids such that the polyunsaturated : saturated fatty acid ratio was greater than 1.0. The second group was advised to consume fatty fish two times/week or 1.5 g EPA, and a third group was to advised to increase their intake of cereal fibre to 18 g/day. The only statistically significant result was a 29% reduction in 2-year all-cause mortality in the group that consumed more fish, as compared with the other two groups. There was a nonsignificant reduction in CAD recurrence in both of the groups advised to alter fat and fish consumption, as compared with the group advised to increase fibre intake alone. Serum cholesterol concentration fell by a very small but statistically significant amount (3.5%) in the group that reduced dietary fat intake, but did not change in the other two groups eating more fish or fibre.

In a more recent intervention [31], over 11,000 coronary patients were randomly assigned to one of four groups for 3–5 years: consumption of n-3 polyunsaturated fatty acids, approximately 1 g/day (EPA : DHA 2:1); vitamin E 300 mg/day; both combined; and no supplementation. There was a 10% reduction in risk for major coronary recurrencies in the n-3 polyunsaturated fatty acids and combined groups, with no advantage of vitamin E supplementation evident. The main effect was due to reduction in coronary (−30%) and sudden deaths (−45%), as well as total deaths (−20%), whereas there was no difference for nonfatal cardiovascular events between the treatment groups. There was no significant change in total cholesterol and HDL-cholesterol, and LDL-cholesterol increased in the n-3 group, whereas serum triglycerides were decreased by 3% from baseline. Accordingly, these results demonstrate an advantageous effect of n-3 polyunsaturated long-chain fatty acids, especially on CAD mortality, without changes in serum cholesterol levels. The beneficial effects are probably due to decreased risk for arrhythmias, improved endothelial function and vascular dilatation, and reduced blood-clotting tendency [10]; the mechanism and role of reduced serum triglycerides need to be clarified further. However, the AHA Dietary Guide-

lines [10] recommend consumption of at least two servings of fish per week, especially fatty fish, in order to benefit from cardioprotective effects.

Lyon Heart Study

This recent intervention [32], which included 605 coronary patients, was conducted to evaluate whether cardiac mortality and morbidity can be reduced by consumption of a Mediterranean-type, α-linolenic acid-rich diet, simulating the most beneficial diet in the Seven Countries Study [2]; in the latter study, this diet was associated with the lowest coronary mortality rate between the various populations studied. The Lyon Heart Study [32] was a randomized, single-blinded, secondary prevention study, in which the intervention group was advised to consume the following: more bread; more root vegetables and green vegetables; more fish; less meat such as beef, lamb and pork, which should be replaced by poultry; more fruit; and margarine, olive oil and rapeseed oil rather than butter and cream. The mean follow-up time was 27 months [32], but this was later extended to a mean of 46 months [33]. Individuals in the intervention group consumed less cholesterol (217 versus 318 mg/day); fewer calories in fat (30.5% versus 32.7%), especially as saturated fat (8.3% versus 11.7%); less α-linoleic acid (3.6% versus 5.3%); but more oleic acid (13% versus 10%), three times more α-linolenic acid (0.8% versus 0.3%) and EPA [32]; and more fibre (19 g/day versus 15 g/day) [33] than did the control population. The polyunsaturated : saturated fatty acid ratio was similar in the groups. The intake of α-tocopherol did not differ between the groups, but ascorbic acid intake was higher in the intervention than in the control group.

At the end of the follow-up period serum lipids and apoprotein B levels did not differ between the groups. However, in both groups serum total cholesterol was reduced by approximately 5%, LDL-cholesterol by 7% and triglycerides by 14%, and HDL-cholesterol was increased by approximately by 10% from baseline. Whether these changes are significant is not obvious from the results. However, it is surprising that the serum cholesterol reductions were not larger in the intervention group, considering the reduced amounts of dietary cholesterol and fat consumed by that group.

There was a significant risk reduction of 73% in primary end-points (cardiac mortality and morbidity) between the experimental and control groups, even though the number of events was low after the first follow-up period (8 versus 33). If all cardiovascular events (ie cardiac death, nonfatal infarction, unstable angina, heart failure, stroke and thromboembolism) were combined, then the survival curves differed between the groups within the first year [34]. After the prolonged follow up, the protective effect of the diet was maintained, and fewer primary end-point events occurred in the experimental group than in the control

group (14 versus 44) [33]. Also, the number of secondary end-points (ie unstable angina, stroke, heart failure, pulmonary or peripheral embolism) was significantly diminished, such that the reduced risk ratios varied from 0.28 for primary end-points to 0.53 for combined total primary, secondary and minor secondary end-points. Furthermore, after the extended follow up, serum lipid values were similar between the groups. In multivariate analysis to examine the impact of various factors on risk reduction, the intervention diet and α-linolenic acid made significant contributions, as did serum cholesterol level, sex, systolic blood pressure and leucocyte count.

The results of the Lyon Heart Study suggest that, with a change in diet, it is possible to reduce the incidence of CAD, and that compliance with new dietary habits is feasible if instructions given to patients and surveillance are properly conducted. Lowering of serum cholesterol level was of similar magnitude in the experimental and control groups, but serum cholesterol level had an independent impact on risk reduction. The specific dietary change in the experimental group was the different fatty-acid profile, and higher fibre intake and ascorbic acid level. What then was the mechanism responsible for the reduction in incidence of CAD? It is well documented that reduction in serum cholesterol level stabilizes the vulnerable plaque by reducing the lipid core. α-Linolenic acid, the second essential fatty acid in humans, can be elongated to the long-chain EPA and DHA, but its other exact functions in the human body are not characterized in detail. It is present in abundance in retinal and brain tissues, but its role for example in in cell membranes or signal transduction is unresolved. Accordingly, its exact mechanism of action in reducing coronary disease recurrence is unknown, but the AHA Dietary Guidelines [10] recommend increasing its daily intake, as for the long-chain n-3 fatty acids from fish. Canola oil, soybean oil and nuts are rich sources of α-linolenic acid.

Plant stanol and sterol esters

Unesterified, mainly crystalline plant sterols have been used since early 1950s in the treatment of hypercholesterolaemia [35]. Fat-soluble plant stanol esters were introduced in 1991 for serum cholesterol lowering [36]. Plant stanol ester margarine (Benecol; Raisio Group plc, Raisio, Finland) has been marketed for that purpose in Finland since 1995, when 1-year cholesterol-lowering results with this product were reported by Miettinen [37]. At present, the product is available in several countries in different fat spreads, and in the form of yogurt, cheese, snack bar and salad dressing. According to recent results [38,39], the plant stanol ester margarine lowers serum total cholesterol by 10–15% and LDL-cholesterol by up to 20%. In addition, the product provides a substitute for the saturated fats in dairy spreads and for increased consumption of the polyunsaturated fatty acids of rapeseed oil (canola oil)

margarine that is the vehicle for the stanol esters. Virtually no harmful side effects have been observed. Plant stanol ester margarine lowers serum cholesterol by inhibiting sterol absorption in general, resulting not only in serum cholesterol, but also in reduction in serum plant sterols. Enhanced elimination of cholesterol stimulates compensatory cholesterol synthesis within the body [35].

During the late 1990s, based on earlier findings of Mattson et al [40], plant sterol ester margarine was found to lower serum cholesterol [41,42]. The reduction in short-term studies was approximately similar to that with the plant stanol esters, and the margarine has been marketed as Becel Pro-Activ (Unilever, The Netherlands). However, plant sterols are absorbed to a markedly higher extent than are plant stanols. Consumption of plant sterol esters, in contrast to that of plant stanol esters, increases serum plant sterol concentrations. In most cases, the increase in levels of plant sterol remains significantly lower than that seen in phytosterolaemia, a hereditary and strongly atherogenic clinical condition [43]. It remains unclear whether this absorption of plant sterols offers any risk of vascular events, because the published studies are of short duration.

Consumption of plant stanol ester margarine lowers serum cholesterol in normal individuals, in slightly hypercholesterolaemic patients, in adults and children with familial hypercholesterolaemia, and in hypercholesterolaemic type 2 diabetic persons [35,38,39]. Cholesterol lowering does not appear to depend on dietary cholesterol intake or fatty acid composition. Consumption of plant stanol and sterol esters does not appear to interfere with absorption of fat-soluble vitamins, even though in the long term serum β-carotene concentration may decrease. The consumption periods of plant stanol and sterol ester studies have been relatively short (1 year for stanol esters and several weeks for sterol esters) and no placebo-controlled intervention trial has been performed concerning their possible capacity to reduce the incidence of coronary events. Therefore, no evidence-based information is available, and it is unclear whether chronic consumption of functional foods with added plant stanol or sterol esters would prevent development of atheromatous coronary disease. A review of the published papers [44] suggests that prevention of coronary events would be approximately 25% with a 0.6 mmol/l (approximately 10%) reduction in serum cholesterol with esterified phytosterols.

A recent long-term simvastatin prevention trial (4S) [15] showed that coronary patients with high baseline cholesterol absorption (defined by high serum cholestanol and plant sterol : cholesterol ratios) did not experience a reduction in incidence of coronary events, whereas those with low absorption were responders [45]. In addition, those with high absorption, in contrast to those with low absorption,

exhibited gradually increased plant sterol levels over a 5-year period and tended to have a lesser cholesterol reduction; these two factors are presumed to contribute to nonresponsiveness to event reduction [46]. It was assumed that additional use of plant stanol esters would be beneficial. In fact, combination of inhibitors of cholesterol synthesis (statins) and absorption (stanol esters) had a clear additive effect on both cholesterol and plant sterol reductions, with statins also eliminating the compensatory increase in cholesterol synthesis caused by stanol esters [47,48]. A combination of stanol ester margarine consumption with long-term statin treatment in individuals with high baseline cholesterol absorption lowered serum cholesterol more consistently than in those with low baseline absorption, and plant sterol reductions were more consistent [49]. In a small, controlled, randomized study (Gylling H, Miettinen TA, unpublished data), treatment of patients with acute myocardial infarction immediately after hospital discharge with stanol ester margarine plus lovastatin lowered serum LDL-cholesterol by almost 50% when compared with a control group that consumed margarine only. In contrast to other preliminary observations in acute coronary syndromes [50,51], clinical coronary events were similar in the two groups during the first posthospital year. This is not unusual, because differences in coronary events are not evident for more than 1 year after cholesterol reduction [15].

Conclusion

By dietary means, it is possible to diminish total and coronary mortality, coronary morbidity, and other atherosclerotic manifestations. The beneficial effects are obtained by lowering serum cholesterol level and stabilizing the plaque, but also by improving the endothelial function, decreasing the risk of arrhythmias and reducing blood-clotting tendency. These results can be obtained by modest and feasible dietary changes, which can be supported by adding plant stanol and sterol esters to the diet. Accordingly, in order to reduce coronary artery disease and to interfere with the atherosclerotic process, a population-based dietary counselling seems to be justifiable.

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