Review article

Diet, hyperlipidaemia and cardiovascular disease

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Reviewed here are results of intervention studies examining relationships between diet and hyperlipidaemia, or diet and cardiovascular disease (CVD). A reduction in the intake of saturated fatty acids (SFAs) and trans-fatty acids (TFAs), and an increase in the intake of polyunsaturated fatty acids (PUFAs), are favourable to lipoprotein status. Where a reduction in total fat intake is achieved by a reduction in dietary SFAs, there would appear to be a favourable effect on CVD events and mortality, although the evidence for this from intervention studies is not strong. Adequate dietary PUFA intake, both ω6 and ω3, may be associated with reduced risk for CVD events more via pathways other than those which operate through lipoproteins. Other macronutrients including carbohydrates, proteins and alcohol can have significant effects on lipoproteins, although the effects of dietary intervention with these nutrients on coronary and total mortality are virtually unknown. Non-nutrient components of foods with small lipid lowering properties may be cumulatively important in an overall diet. In relation to food, results of secondary intervention studies provide support for a beneficial role of plant food and fish in reducing coronary and total mortality. Therefore as far as both hyperlipidaemia and CVD are concerned, the total dietary approach may be more important than the single nutrient approach.

Introduction

Dietary modification of serum lipoproteins is usually intended to reduce cardiovascular and total mortality. Available studies deal with the way diet changes serum lipoproteins, as well as atherosclerosis, coronary artery disease (CAD), myocardial infarction (MI), and mortality. Dietary management of hyperlipidaemia therefore concerns not only the modification of serum lipoproteins, but more importantly the prevention of cardiovascular disease (CVD) and mortality.

The majority of studies which have examined relationships between diet and CVD or CVD risk factors have emphasised the fat component of the diet. Other dietary components, including protein, carbohydrate, vitamins, minerals and non-nutrient components of food may affect serum lipoproteins and CVD risk. However, in most populations the quantity and quality of fat in the diet is believed to be a powerful dietary indicator of CVD risk.

The evidence reviewed here includes intervention studies which have examined the relationship between diet and serum lipids and lipoproteins, as well as CVD end points. Where information from intervention studies is limited, evidence from prospective, cross-sectional and case-control studies is examined.

Diet and cardiovascular disease: an introduction

The "diet-heart" hypothesis was proposed to explain the relationship between diet, fatty acids in particular, and CVD. According to this hypothesis, a high intake of saturated fatty acids (SFAs) and cholesterol and a low intake of polyunsaturated fatty acids (PUFAs) increases serum cholesterol, which leads to the development of atheromatous plaques in the coronary arteries. Accumulation of these plaques leads to narrowing of the coronary arteries, reduced blood flow to the heart muscle, and finally to the occurrence of MI[1]. This hypothesis is supported by two lines of evidence: studies which have associated dietary fatty acids with serum cholesterol concentrations, and studies which have found a positive association between serum cholesterol concentration and CVD. Various other dyslipidaemias, including low high-density lipoprotein (HDL) cholesterol concentration, raised serum triglyceride concentration, increased serum concentration of small dense low-density lipoprotein (LDL) particles, and poor chylomicron remnant clearance, have now been associated with increased risk of CVD. Dietary fatty acids have also been related to CVD risk through these other dyslipidaemias. These developments have altered the hypothesis to include many other aspects of lipid and lipoprotein metabolism.

The key role which thrombosis plays in CVD was not included in the "diet-heart" hypothesis, and until recently thrombosis was regarded separately to the process of atherosclerosis. The development of coronary thrombosis as a result of fissuring of an atherosclerotic plaque is the major determinant of progression of stable atherosclerotic lesions to MI[2]. Thrombosis may also be involved in atherosclerotic plaque development. Atherosclerotic plaques may increase in size after rupturing and thrombus formation[3]. Furthermore, lipoproteins might influence thrombosis via effects on coagulation, in addition to their role in atherosclerosis[4]. Dietary fatty acids have also been linked to thrombosis[3]. Omega-3 fatty acids in particular have been shown to be antithrombotic. However, there is no clearly established prothrombotic effect of saturated

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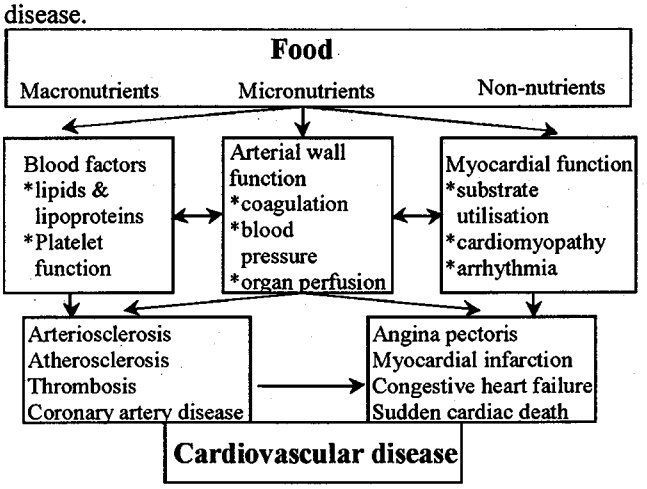
fatty acids, although this has not been ruled out[5].

The role of diet in CVD has been summarised briefly in Figure 1. Blood factors, including lipoproteins and platelet function, and arterial wall function, with its effects on coagulation, blood pressure, and organ perfusion influence the processes of arteriosclerosis, atherosclerosis and thrombosis, which can lead to CAD. Coronary artery disease, along with these other processes may result in angina, MI or death. Diet may also influence CVD through pathways other than atherosclerosis and thrombosis[6]. For example CVD may result from poor myocardial function. Particular micronutrients, including selenium deficiency[7] and cobalt toxicity[8] may lead to cardiomyopathy, impaired myocardial function, and congestive heart failure. There is also evidence that myocardial function can be influenced by dietary fat[9,10], and alcohol[11].

Figure 1. Potential pathways linking diet to cardiovascular disease.



In relation to CVD, most intervention studies have investigated links between diet and hyperlipidaemia, hyperlipidaemia and CVD end points, or diet and CVD end points presumed to be operating through hyperlipidaemias. Outlined in Figure 1 are several other pathways through which diet might influence CVD. The importance of these pathways to CVD is recognised, and it is recognised that many of the changes in CVD produced by dietary intervention may relate to pathways other than those which operate through serum lipids and lipoproteins. The main focus in this review, however, is the diet-hyperlipidaemia-CVD pathway.

The nature of diet

Diet or food intake may be described, or changed, in terms of foods or nutrients. Most dietary intervention studies have examined one particular nutrient, namely fat, but other dietary components including protein, carbohydrates, dietary fibre and alcohol have also been studied. Few studies have used foods such as plant-derived or fish as the dietary intervention. Even here, the assumption in studies of food intervention is that specific nutrient effects are usually in question. However, foods contain more than one nutrient, and indeed many non-nutrients of biological importance. Some of the effects observed may therefore be due to other factors in food, although the evidence for certain nutrient relationships is quite strong. Secondary dietary changes resulting from the desired intervention should also be taken into account. For example, a reduction in the total fat intake will usually result in changes in carbohydrate and/ or protein intake.

Predicting dietary responsiveness

Not all individuals will respond to the same dietary change with the same change in serum lipoprotein status, let alone in cardiovascular event or total mortality end points. There are several reasons for these differences which need to be taken into account in the evaluation of intervention studies. The background diet of the study community or individual is one of the most important considerations. In addition, there are genetic determinants of hyperlipidaemia or atherosclerosis susceptibility. These include familial hypercholesterolaemia which is usually poorly responsive to diet, although ordinarily LDL receptors are responsive to dietary change[12]. Apo E status is indicative of responsiveness of serum lipids to dietary fat change, with apo E_4 being more responsive than apo E_3[13,14]. There are also non-dietary lifestyle factors such as physical inactivity and cigarette smoking which may influence dietary responsiveness.

Energy balance and hyperlipidaemia

Increased body fatness represents positive energy balance, whether for reasons of excessive intake or under-expenditure. Over fatness and an abdominal distribution of fatness are the most potent factors in increasing VLDL triglyceride and LDL cholesterol and decreasing HDL cholesterol[15]. An increasing prevalence of obesity (body mass index >30 kg/ m_2) in the Australian population during the 1980s is therefore of considerable importance[16].

Dietary fat and hyperlipidaemia

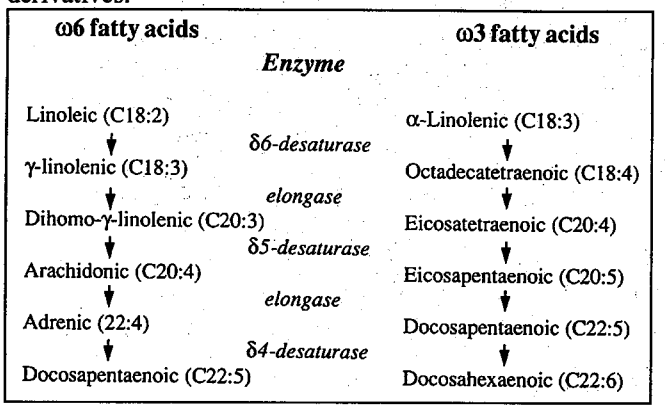
Introduction

Dietary fat may be derived from animal or plant sources. The most abundant type of dietary fat is triglyceride, which may provide SFA, monounsaturated fatty acids (MUFA), and PUFA. Most PUFAs in the diet are essential fatty acids (EFA) or EFA derivatives. There are two classes of EFAs, omega-6 (ω6) and omega-3 (ω3). Linoleic acid (18:2ω6) and α-linolenic acid (18:3ω3) are the precursor or parent ω6 and ω3 EFAs, from which longer chain EFAs are derived by enzyme desaturation and elongation. The same group of enzymes are shared between fatty acid classes (Fig. 2). SFAs and MUFAs are not essential, because humans possess the ability to derive these from protein and carbohydrate if necessary. Although *trans*-fatty acids (TFA) can be classed as either MUFA or PUFA, they are often classified as a separate group because most unsaturated fat, both dietary and *in vivo* derived, in humans is in the *cis* configuration. The fatty acid classes can also be described in terms of individual fatty acids. This is useful when different fatty acids within one class have different metabolic effects. Cholesterol and phospholipids are also important dietary fats.

Hyperlipidaemia has been classified as type IIA (raised LDL cholesterol), type IIB (raised LDL cholesterol and raised VLDL, characterised by an elevated fasting serum

triglyceride measurement), or type IV (raised VLDL only). More recently, the term dyslipidaemia has been used to describe hyperlipidaemias as well as low HDL cholesterol concentration, raised serum triglyceride concentration, increased serum concentration of small dense LDL particles in serum, and poor chylomicron remnant clearance.

Figure 2. Metabolic pathways for the conversion of ω6 and ω3 essential fatty acids to essential fatty acid derivatives.



Fatty acid classes

In one of the earliest studies on dietary fat and serum cholesterol, Kinsell et al[17] found that diets high in vegetable fat lowered serum cholesterol concentrations, findings that were confirmed in the same decade[18-23]. These studies established that serum cholesterol concentrations were more upwardly responsive to dietary saturated fat than to total fat or cholesterol in the diet. After comparisons of different fats and oils in these studies, it was proposed that SFAs were responsible for a hypercholesterolaemic effect, and that PUFAs were responsible for a hypocholesterolaemic effect[18,21,23]. Formulae to predict the expected change in serum cholesterol with changes in SFAs, PUFAs, and cholesterol were developed separately by Keys et al [22,24,25] and Hegsted et al [26,27]. A recent meta-analysis of 27 trials[28], on the effects of dietary fatty acids on serum lipids and lipoproteins produced an equation which was in close agreement with those of Keys et al and Hegsted et al.

These studies showed that serum cholesterol is much more responsive to changes in dietary SFAs than either dietary PUFAs or cholesterol. In the studies by Hegsted et al[26] the changes in SFAs accounted for over 70% of the variations in serum cholesterol. Dietary cholesterol has a significant, although minor contribution to serum cholesterol changes. Although both the equations of Keys et al[25] and Hegsted[27] were able to predict well the effects of changes in dietary fat on serum cholesterol, several investigators have found large individual variability in response to changes in dietary SFAs, PUFAs[24,29], and especially to dietary cholesterol[30,31].

The question of the appropriate ratio of PUFAs to SFAs (P:S ratio) has been addressed by Gustafsson et al[32,33]. In these studies, diets with different P:S ratios were compared with respect to serum lipoprotein changes. It was found that increasing the P:S ratio above 0.7 did not improve serum lipoproteins in patients with moderate hyperlipidaemia. Most of the benefits in relation to the lipoproteins were therefore gained with a shift in the P:S ratio up to 0.7. However, this level might depend upon factors affecting dietary responsiveness.

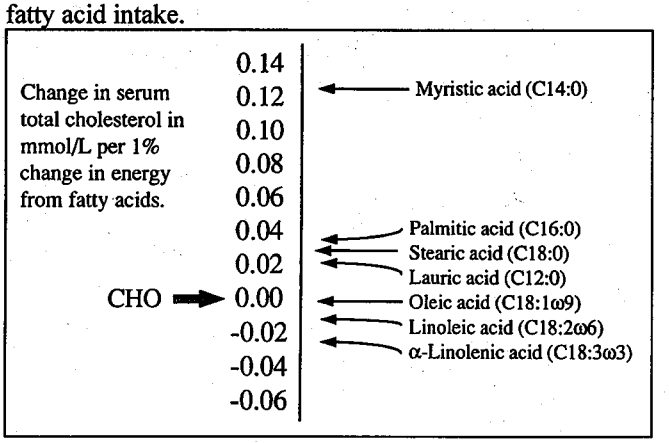
There is also evidence in support of the relationship between increasing the P:S ratio and improving serum lipoproteins in a large scale study. In the Lipid Research Clinics Primary Prevention Trial, in which over 6000 hypercholesterolaemic men were advised to adopt a diet lower in SFAs and cholesterol and relatively higher in PUFAs, SFAs were directly related and PUFAs were inversely related to LDL cholesterol lowering[34].

Apart from the specific fatty acid composition of the diet, several other dietary factors are important determinants of effects on serum lipids and lipoproteins. The most important of these is probably the background diet. The prevailing level of SFAs in the diet, for example, might influence the degree to which a reduction of SFAs will reduce LDL cholesterol. In addition, the structure of the triglyceride in the fat being consumed can also influence serum lipid and lipoprotein responses[35,36].

Saturated fatty acids

Myristic acid (C14:0) has the greatest cholesterol elevating effects[25,26] and has been estimated to be four to six times as cholesterol raising as either lauric (Cl2:0) or palmitic (C16:0) acid[37]. However, the effects of individual fatty acids on serum cholesterol can still only be estimated. Refinement of the Keys and Hegsted equations is proceeding with more metabolic studies. The more recent studies indicate that a change in palmitic acid intake has relatively little effect on LDL cholesterol concentration, particularly when compared to change in myristic acid ingestion[38-40]. A number of experiments have indicated that stearic acid (C18:0) does not elevate cholesterol[25,26,41]. Saturated fatty acids of chain length less than C10 produce little or no cholesterol elevation [25,42,43]. These results are summarised in Figure 3.

Figure 3 Response of serum total cholesterol to changes in fatty acid intake.



Estimates taken from meta-analysis of Mensink and Katan (28). Figure adapted from Grundy (44).

Monounsaturated fatty acids (MUFAs)

The major MUFA in the diet is oleic acid (18:1 n-9). It is widespread in the food supply, the richest sources being olive oil and canola oil. The effects of MUFAs on serum cholesterol have been examined in a number of studies[45-47], and it was found in all of these studies that MUFAs did not elevate serum cholesterol concentrations as did SFAs, and that diets high in MUFAs did not lower HDL cholesterol concentrations, as did substitution of SFAs with carbohydrates. It has been estimated from a meta-analysis[28] that if monounsaturated fatty acids replace carbohydrate in the diet then a relatively small decrease in LDL cholesterol and a small increase in HDL cholesterol is expected.

Polyunsaturated fatty acids (PUFAs)

Although increasing linoleic acid will lower LDL cholesterol, its effects are less than half that of lowering dietary saturated fatty acids[28]. The serum cholesterol lowering potential of linoleic acid is shown in Figure 3.

Fish and fish oils are major sources of omega-3 (ω3) fatty acids. Fish oils consistently reduce serum triglyceride concentrations, particularly in hypertriglyceridaemic subjects[48-50]. Although substitution of SFAs with long chain ω3 PUFAs has been found to result in a fall in total cholesterol[19,21] and LDL cholesterol, this effect seems to be due to reduced SFAs. Supplementation with ω3 PUFAs has also been reported not to lower LDL cholesterol[51], and lowering of serum triglycerides with fish oils is often associated with an increase in LDL cholesterol[52], particularly in association with diabetes[53]. However, different ω3 PUFAs may have different effects on serum cholesterol concentrations.

Fish oils also affect the haemostatic system and eicosanoid metabolism. The overall result of an increase in the intake of ω3 fatty acids is a beneficial change in the haemostatic balance towards a more vasodilatory state, with reduced platelet aggregation. There is evidence that much of the proposed beneficial effects of the ω3 fatty acids on cardiovascular disease may operate through the haemostatic system and eicosanoid metabolism rather than through lipoproteins, thereby reducing the risk of MI through influencing thrombosis.

Trans-fatty acids (TFAs)

Many vegetable oils require partial hydrogenation to attain properties needed for particular food uses. This process generates a variety of *trans* and uncommon *cis*-fatty acid isomers. The other major source of TFAs is from ruminant animal origins.

A number of studies have examined the relationship between TFAs in the diet and serum lipids and lipoprotein concentrations. Many of these studies, conducted during the 1960s, produced inconsistent findings. More recently, well-designed studies have found that TFAs increase LDL cholesterol[54,55] and Lp(a)[38,56], and reduce HDL cholesterol[54,55], and overall are approximately as unfavourable on serum lipoproteins as SFAs in general. It is not known whether particular TFAs are responsible for the observed effects.

Modification of other macronutrient intakes and hyperlipidaemia

Carbohydrates

The effects of dietary fatty acids on serum lipids and lipoproteins are often measured in relation to carbohydrate intakes, which are assumed to be neutral in these analyses. However, high carbohydrate diets reduce LDL cholesterol[46], although their beneficial effects seem to be secondary to a reduction in dietary SFAs. High carbohydrate diets may also be associated with increased VLDL production and elevated triglyceride levels, and falls in HDL cholesterol[28,57]. It must be kept in mind however, that serum lipoproteins are not the most important outcome. Cardiovascular disease and death are obviously more important.

Protein

There is some evidence which suggests that the source of protein (animal vs plant) has differential effects on serum lipoproteins. Soy protein based diets have been shown to lower serum LDL cholesterol in hyperlipidaemic subjects[58-61]. However, the effect is less consistent in normocholesterolaemic people[62-64].

Alcohol

Alcohol consumption produces an increase in serum triglyceride concentrations as a result of elevation of VLDL and chylomicron levels[65]. There is also some elevation of serum cholesterol levels. A proportion of this is due to an increase in HDL cholesterol[66,67]. The rise in HDL cholesterol occurs only in inactive individuals, not in runners where HDL levels are already raised[68].

There is also some evidence for an inverse association between alcohol intake and LDL cholesterol. In the Lipid Research Clinics Coronary Primary Prevention Trial, change in alcohol intake was associated inversely with change in LDL cholesterol levels among men in the placebo group after adjustment for body mass index and dietary lipids[69].

Fibre

Numerous studies have suggested that an increased consumption of fibre-rich foods can reduce serum cholesterol levels[70-72]. However, not all dietary fibre appears to influence serum lipoproteins. Insoluble fibre (such as wheat bran) has little influence on serum lipoproteins[73]. Soluble fibres appear to favourably affect serum lipoproteins. However, the effects are variable depending on the type of soluble fibre used. For example, guar gums tend to lower LDL cholesterol, but not influence HDL cholesterol, whereas oat bran will lower LDL cholesterol as well as increase HDL cholesterol[74]. Oat bran may also lower triglycerides in hypercholesterolaemic people[75].

Micronutrients

Niacin in doses used to lower serum cholesterol should be regarded as a pharmacological rather than a nutritional approach. There is little evidence that other micronutrients can influence serum lipid and lipoprotein concentrations. However, there may be several micronutrients which

influence atherosclerosis via effects on lipoproteins without significantly altering lipoprotein concentrations[76].

Non-nutrient food components and hyperlipidaemia

There is growing interest in various non-nutrient components of food which favourably influence plasma lipoprotein status. At the moment, these identified components should be regarded as indicative of new ways of looking at food from the point of view of the management of hyperlipidaemia. The components include:

- a lipid soluble fraction from boiled coffee[77],
- allicin from garlic[78,79],
- saponins from foods like chick peas[80],
- tocotrienols from barley and palm oil, which appear to have HMG CoA reductase inhibitor activity[81,82]
- and plant sterols which may be handled alternatively to cholesterol[83].

With the growing evidence for physiological effects of phytoestrogens in humans[84] and serum cholesterol-lowering properties in experimental animals of certain natural food colours like anthocyanins[85,86], there may be an ever wider range of foods of value in the management of lipid disorders. Although the effects of individual food components may be relatively small (say a 1-3% lowering of LDL cholesterol) cumulatively, several components could be important.

Diet and cardiovascular disease

Cardiovascular end points which have been used in dietary intervention studies include CAD, MI, CVD mortality, and total mortality.

Coronary artery disease

Coronary angiography has been used to assess CAD progression or regression in humans in several studies. However, detailed analysis of nutritional variables, including fatty acids, has only been performed in two quantitative angiographic studies[87,88].

The influence of diet on the appearance of new lesions in human coronary arteries was examined in the placebo arm of the Cholesterol Lowering Atherosclerosis Study (CLAS) study by Blankenhorn et al[89]. Coronary angiograms along with 24-hour dietary recall information were used to examine the relationships between change in diet and the appearance of new lesions. The placebo group was given dietary goals: to reduce total fat to less than 26% (5% SFAs, 10% MUFAs and 10% PUFAs). It was found that increased intake of total fat, PUFAs, linoleic acid (18:2ω6), oleic acid (18:1ω9), and lauric acid (12:0), was associated with a significant increase in risk of new lesions. The results in this study indicated that when total dietary fat and SFAs are reduced, the preferred substitutes may be protein and carbohydrate rather than PUFAs and MUFAs[89].

More comprehensive dietary data was collected in the St Thomas' Atherosclerosis Regression Study (STARS)[90]. Dietary assessments were performed using a dietary history method on all patients at least twice during the study. Pooled data from the usual care and lipid lowering diet groups were used to assess the relationships between nutrient intake and CAD. Total fat and SFA were the nutrients most closely (positively) associated with CAD progression. MUFAs were also positively associated with CAD progression, but this may have been due to a close relationship with total and SFA intake. PUFAs were not significantly related to CAD progression.

Other angiographic trials with dietary interventions, with or without additional interventions[91-93], are in general agreement with the CLAS[89] and STARS[90], and indicate that lower total and saturated fat intakes may result in reduced progression, or regression of CAD. The results are also consistent with an effect of SFA intake on atherosclerosis operating through serum lipoproteins. The relationships of MUFAs and PUFAs with CAD progression is less clear. The lack of a negative relationship between PUFAs and CAD progression in the STARS[90], and the positive relationship between both PUFA and linoleic acid intake and CAD in the CLAS[89] suggests that SFAs may be more important in relation to CAD. The results of the CLAS[89] are consistent with results from a recent cross-sectional study where a positive relationship between linoleic acid and CAD was found[94]. The results from both the STARS[90] and the CLAS[89] are at variance with data finding negative relationships between linoleic acid and CVD events[95-97]. These varying results may reflect a beneficial influence of dietary PUFAs, including linoleic acid, on processes other than atherosclerosis which influence CVD events.

Cardiovascular disease events and mortality

Primary intervention trials

Studies of diet as the only intervention, aiming for a

Table 1. Primary prevention trials of dietary intervention aiming for a reduction in cardiovascular mortality or incidence.

Study/ Author	Randomised	Study Population	Diet	Cholesterol Reduction	Major Findings
Los Angeles Veterans Administration Study Dayton et al 1969	Yes	846 men aged 55 to 89	High P:S ratio	13% (7 years).	31% reduction in all cardiovascular events No reduction in total mortality
Finnish Mental Hospital Study Miettinen et al 1972	No (Cross-over)	1900 men	High P/S ratio(1.42-1.78)	15% (12 years).	Reduced mortality from CHD No reduction in total mortality
Minnesota Coronary Survey Frantz et al 1989	Yes	4393 men & 4664 women	High P:S ratio (0.28[control] c.f1.67[treatment])	15% (1 year)	No significant reduction in CVD events, CVD mortality or total mortality

reduction of cardiovascular mortality and/ or CVD incidence are presented in Table 1. Few primary intervention trials have included changes in diet as the only intervention[98-100]. In the study by Dayton et al[98], the effects were examined of two diets containing about 40% of energy from fat, but with less SFAs and more PUFAs in the experimental diet than the control diet. The experimental diet, which contained 35 to 40% of total fat intake, each of linoleic and oleic acid, reduced serum cholesterol by 12.7%. The experimental diet was associated with a 31% reduction in all atherosclerosis related events There was little difference in total mortality rates, however.

Another of the diet-only primary intervention studies was the Finnish Mental Hospital Study[100]. The mortality from CHD and other causes was studied in a controlled trial with cross-over design. In one hospital a cholesterol lowering diet was introduced, with a PUFA to SFA ratio of 1.42 to 1.78, and in the other hospital a usual diet, with PUFA to SFA ratio of 0.22 to 0.29, served as the control. After six years, the diets were reversed and the trial continued for a further six years. In men, the high PUFA diet was associated with reduced mortality from CHD. Total mortality was also lower on the experimental diet, but not significantly. For women, the differences for both CHD mortality and total mortality were not significant.

In a study by Frantz et al[99], two diets with similar total fat (39% [control] and 38% [treatment]) and MUFA (16% and 18%) intakes, but with differing SFA (18% and 9%), PUFA (5% and 15%) and cholesterol (446 mg and 166 mg) intakes, were compared with respect to CVD events, CVD mortality and total mortality. No differences were observed for any of the end points between the two diets.

Other dietary intervention trials aiming for a reduction in CVD incidence and/ or mortality have considered other CVD-risk factors as well as dietary change, where the effect of dietary change is often confounded with other factors.

Secondary intervention trials

Several secondary intervention trials have been conducted (Table 2). In three of the most successful of these trials, in relation to CVD events, CVD mortality and total mortality, the aim of the successful intervention was to alter the intake of a particular food, foods or diet in general[101-103]. Most of the studies which have failed to show a reduction in events or mortality used an intervention which focused on reducing total fat or increasing the P:S ratio[104-107].

Table 2. Secondary prevention trials of dietary intervention aiming for a reduction in cardiovascular mortality or incidence.

Study/ author	Randomised	Study Population	Diet	Cholesterol Reduction	Major Findings
Morrison[114] 1955	No	100 subjects aged 40-79 years	Low fat	29%	Reduced mortality
Rose et al al 1965	Yes	52 subjects aged <70 years	Low fat added corn and olive oils	Corn oil 20% Olive oil no change	No reduction in mortality between the groups
MRC 1965	Yes	252 subjects aged <65 years	Low fat	8% (3 years)	No reduction in morbidity or mortality
MRC 1968	Yes	393 subjects aged <60 years	High P:S ratio soya-bean oil(2.0)	17% (at 3 years)	Reduced relapse rate No reduction in cardiovascular mortality, or total mortality
Leren[115] l970	Yes	412 subjects aged 30-64 years	High P/S ratio (2.4)	14% (5 years)	Reduced mortality due to myocardial infarction. No difference in total mortality
Bierenbaum[116] et al 1973	No (matched controls)	200 subjects aged 30-60 years	High P:S ratio. (2.6)	10% (10 years).	Reduced mortality from myocardial infarction. And reduced total mortality
Woodhill et al 1978	Yes	458 subjects aged 30-59 studied for 2-7 years	High P:S ratio (1.5)	Intervention. 11%. Controls 7%	No difference in mortality
Burr et al 1989	Yes	2033 men studied for 2 years	Low fat, high fibre, or increased fish intake		29% reduction in all cause mortality in those on the increased fish intake
Singh et al 1992	Yes	406 subjects	Advice to eat fruits, nuts, vegetables, pulses, & fish	Intervention 13% Controls5 %	39% reduction in cardiac events, 45% reduction in total mortality
de Logeril et al 1994	Yes	605 subjects	Advice to eat a "Mediterranean" diet, high in bread, fruit, vegetables & fish; less red meat; butter & cream replaced with high 18:3ω3 margarine	Intervention 5% Control 5%	Significant reduction in CVD deaths & total mortality

In a randomised controlled study by Burr et al[101], the effects of dietary intervention on secondary prevention of myocardial infarction were examined. It was found that an increased intake of fatty fish reduced 2 year all causes mortality by 29%. In another secondary prevention study in patients with recent MI, CVD events and total mortality were significantly reduced with dietary intervention[103]. The dietary intervention which was associated with lower mortality was advice to include more fruit, nuts, vegetables, grain products, and fish in the diet. This advice was associated with significantly lower SFA and MUFA intakes, and significantly higher PUFA intake, as well as a significant reduction in weight. Other macronutrient and micronutrient differences were also observed[103]. In the study by de Logeril[102], mortality was significantly lower in an intervention group who were encouraged to adopt a "Mediterranean-type" diet: more bread, root vegetables, green vegetables, fruit and fish; less red meat; and with butter and cream to be replaced by a canola oil based margarine high in α-linolenic acid (C18:3ω3). After intervention, this group consumed significantly less fat, SFAs, cholesterol, and linoleic acid, and more oleic and α-linolenic acid. The authors contributed much of the reduction in mortality to the increased α-linolenic acid, however, other dietary changes are likely to have contributed to the reduced mortality. The mechanisms for the observed reductions in total mortality in the studies by Burr et al[101], Singh et al[103] and de Logeril et al[102] may have been many and related to the effects of ω3 fatty acids on blood factors, arterial wall function and myocardial function (Fig. 1). Alterations in lipoproteins and atherosclerosis may have been involved, but were probably less important than other pathways.

Recently Truswell[108] performed a meta-analysis on dietary intervention studies and their effects on CVD events, CVD mortality and total mortality. Although most have failed to show a significant effect of intervention on CVD mortality or total mortality, it was estimated from this analysis that the relative risk of death from all causes was 0.94 (95% CI: 0.894-0.988), a significant reduction. The intervention in these trials varied, and included low fat, altered fat, increased fish, altered diet in general, smoking cessation or exercise, or a combination of these. It is therefore difficult to attribute the reduced mortality to specific dietary factors. However, the results do suggest that dietary intervention can reduce total mortality.

Foods and cardiovascular disease. prospective studies

Prospective studies have shown that many dietary interventions can favourably influence serum lipid and lipoprotein concentrations. Diets low in total and SFAs, and with sufficient ω6 and ω3 PUFAs; relatively high in carbohydrate and protein; low in alcohol; and with a variety of plant foods with various lipid lowering properties will favourably modify most dyslipidaemias. Prospective studies also show that people who have a higher energy intake[109-112] indicative of greater physical activity, a high plant food intake[109], and a higher intake of fish[113] have lower risk of CVD.

Conclusion

It is evident from intervention studies that diet can influence hyperlipidaemia. A positive energy balance, characterised by obesity and abdominal obesity, is one of the most powerful factors in increasing serum LDL cholesterol and triglyceride concentrations, and decreasing HDL cholesterol concentration. Of the macronutrients, dietary fat has the most potent effect. A reduction in the intake of SFAs and TFAs, and an increase in the intake of PUFAs, have favourable effects on LDL and HDL cholesterol, and triglyceride concentrations. Other macronutrients can also have significant effects on lipoproteins. High carbohydrate diets reduce LDL cholesterol and HDL cholesterol, and may increase triglyceride levels. Some of these effects may be secondary to changes in dietary fat intake. It is still not clear whether the type of protein in the diet can have significant effects on serum cholesterol and triglyceride concentrations. Soluble fibres appear to favourably affect serum LDL cholesterol, and some may increase HDL cholesterol and lower triglycerides. Numerous non-nutrient components of food have been identified as having minor lipid lowering properties. Cumulatively, these may be important in the overall diet.

Diet has also been shown to alter CVD risk. The mechanisms involved may be many, and relate to factors other than hyperlipidaemia. Where a reduction in total fat intake is achieved by a reduction in dietary SFAs, there would appear to be a favourable effect on CVD events and mortality, although the evidence for this from intervention studies is not strong. The mechanisms implicated here are probably related to the hyperlipidaemia-atherosclerosis link. Higher dietary PUFA intake, of both ω6 and ω3, may be associated with reduced risk for CVD events, perhaps more through thrombosis and other processes than atherosclerosis. The effects of dietary intervention with carbohydrates, protein, alcohol, fibre, various micro-nutrients, or different non-nutrients, on coronary and total mortality is virtually unknown. There is, however, growing evidence that higher plant food intakes, and therefore carbohydrate intakes, may favourably influence CVD. In relation to food, results of secondary intervention studies provide support for a beneficial role of plant food and fish in reducing coronary and total mortality. This view is supported by results of prospective studies. Therefore as far as both hyperlipidaemia and CVD are concerned, the total dietary approach may be more important than the single nutrient approach.

Diet, hyperlipidaemia and cardiovascular disease

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膳食、高脂血症及心血管疾病

摘要

本文評論了膳食與高脂血症或膳食與心血管疾病（CVD）間的關係。減少飽和脂肪酸（SFAS）和反式一脂肪酸（TFAS），並增加多不飽和脂肪酸（PUFAS）的進食，對脂蛋白狀況有利。雖然研究數據仍未充足牢固，但以減少膳食飽和脂肪酸來達到降低總脂肪進食，將對心血管疾病和死亡率產生有利的影響。進食足夠的多不飽和脂肪酸，包括 W_6 和 W_3 脂肪酸也許會使心血管疾病的危險減少。雖然碳水化合物、蛋白質和酒精對冠心病和總死亡率的影響仍未明確，但這些宏量營養素能對脂蛋白有明顯影響是肯定的，食物中具輕微降脂類特性的非營養素成份在總體膳食中也許是重要的。與食物有關，植物性食物和魚類在減少冠心病和總死亡率起到有益的作用是得到研究的支持。所以就高脂血症和心血管疾病而論，整體膳食的探討也許較之單一營養素的探討更爲重要。

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