Dietary management of hyperlipidaemia: impact on cardiovascular disease and all cause mortality

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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, tissue ischaemia, infarction or its complications, and mortality. Dietary management of hyperlipidaemia therefore concerns not only the modification of serum lipoproteins, but more importantly the prevention of cardiovascular disease and mortality.

The evidence reviewed here will include intervention studies which have examined the relationship between diet and serum lipoproteins or cardiovascular disease (CVD) end points. Where information from intervention studies is limited, evidence from prospective studies will be examined.

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 nutrients 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. Some of the reasons for these differences which need to be taken into account in the evaluation of intervention studies, or of individual patient treatment include:

- The **background diet** of the study community or individual. This is best described as centile distributions of food and of nutrient intakes in a community, and where an individual fits in that community (Baghurst et al 1987, 1988). In this way differences in health response to dietary change between communities and between individuals can be compared in a more understandable way.

  Further, in a society pluralistic for food culture, as with the ethnic diversity in Australia, there can be quite different effects of particular food changes on coronary risk factors, depending on the way in which food is prepared and eaten (Hage et al 1991).

- **Genetic determinants** of hyperlipidaemia or atherosclerosis susceptibility. For example:

  - Familial hypercholesterolaemia is usually poorly responsive to diet although ordinarily LDL receptors are responsive to dietary change (Goldstein and Brown 1983).

  - apo E status is indicative of responsiveness of serum lipids to dietary fat change, and apo E_4 being more responsive than apo E_3 (Miettinen 1991, Savolainen et al 1991).

- **Non-dietary lifestyle factors** are critical such as:

  - physical inactivity which may be associated with higher VLDL–triglyceride and lower HDL–cholesterol;

- alcohol intake which may contribute to hypertriglyceridaemia and higher HDL–cholesterol; and
- cigarette smoking which can lead to lower HDL–cholesterol.

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 of all in increasing VLDL and LDL and decreasing HDL (Björntorp and Smith 1987). And increasing prevalence of obesity (Body Mass Index >30 kg m^{-2}) in the Australian population during the 1980s is therefore of considerable importance (NHF Risk Factors Prevalence Survey 1983, 1989).

Dietary fat and hyperlipidaemia

Dietary fat may be derived from animal or plant sources. The most abundant type of dietary fat is triglyceride, which may provide saturated, monounsaturated, and polyunsaturated fatty acids. 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). Management of hyperlipidaemia therefore takes into account LDL cholesterol and triglycerides, and should also consider HDL cholesterol levels.

Clinical studies examining the effects of changes in dietary fat on serum lipoproteins have either been under metabolic ward conditions or in free living populations. Many of the early studies were conducted under metabolic ward conditions. The large population studies which also included cardiovascular end points were on free living subjects.

In one of the earliest studies on dietary fat and serum cholesterol, Kinsell et al (1952) found that diets high in vegetable fat lowered serum cholesterol concentrations. These findings were confirmed in the same decade (Ahrens et al 1957, 1959, Bronte-Stewart et al 1955, Keys et al 1957a,b, Malmros and Wigand 1957). These studies established that serum cholesterol concentrations were more 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 saturated fatty acids (SFAs) were responsible for a hypercholesterolaemic effect, and that polyunsaturated fatty acids (PUFAs) were responsible for a hypocholesterolaemic effect (Ahrens et al 1957, Keys et al 1957a, Malmros and Wigand 1957). Formulas to predict the expected change in serum cholesterol with changes in SFAs, PUFAs, and cholesterol were developed separately by (i) Keys et al (1957b, 1959, 1965a) and (ii) Hegsted et al (1965), Hegsted (1986). Two of these equations are given below:

serum cholesterol change = 1.35 (2S - P) + 1.52Z (Keys et al 1965a)

serum cholesterol change = 2.16S - 1.65P + 0.097C (Hegsted 1986)

S = Change in the percentage of calories from saturated fat.

P = Change in the percentage of calories from polyunsaturated fat.

Z = The difference between the square root of the initial intake of choleste4rol and the square root of the subsequent intake of cholesterol.

C = The difference between the cholesterol intake of two diets in mg/1000 kcal.

It can be seen from both equations 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 (1965) the changes in SFAs accounted for over 70 per cent of the variations in serum cholesterol. Dietary cholesterol has a significant, although minor contribution to serum cholesterol changes. Although both equations were able to predict over 90 per cent of 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 (Keys et al 1959, 1965b), and especially to dietary cholesterol (Grundy and Vega 1988, Katan et al 1988).

The question of the appropriate ratio of PUFAs to SFAs (P:S ratio) has been addressed by Gustafsson et al (1983, 1985). 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, are therefore gained with a shift in the P:S ratio up to 0.7.

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 6 000 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 (Gordon et al 1982). The associations between dietary fat changes and serum lipoproteins are now examined further in terms of specific fatty acids.

Saturated fatty acids

The most hypercholesterolaemic of the SFAs are those of chain length C12 to C16. Certainly myristic acid (C14) has cholesterol elevating effects (Keys et al 1965a, Hegsted et al 1965). Lauric acid (C12) also raises serum cholesterol, however the extent of its effects are unclear. A number of experiments have indicated that stearic acid (C18:0) does not elevate cholesterol (Keys et al 1965a, Hegsted et al 1965, Bonanome and Grundy 1988). Saturated fatty acids of chain length less than C10 produce little or no cholesterol elevation (Beveridge et al 1959, Hashim et al 1960, Keys et al 1965a). These results are summarised in figure 1.

Refinement of the Keys and Hegsted equations is proceeding with more metabolic studies. Recent work of Hayes et al (1991a,b) indicates that a change in 16:0 fatty acid intake is relatively neutral for LDL cholesterol compared with change in 14:0 fatty acid ingestion, which may have been underestimated as a cholesterol raising fatty acid.

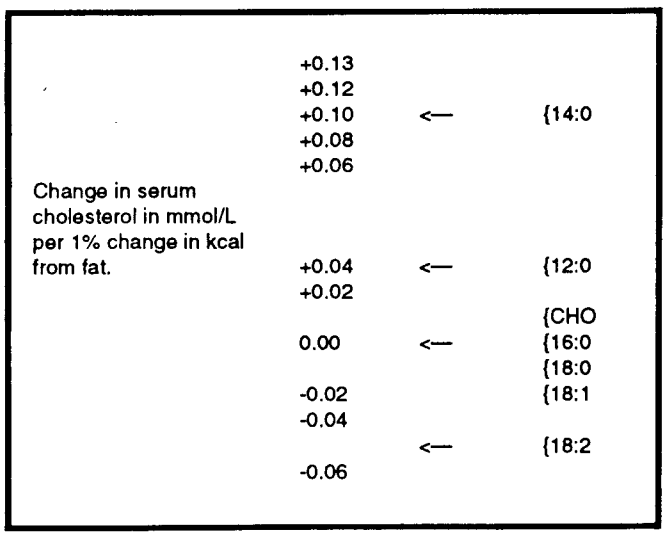

Fig 1. Responses to changes in dietary fatty acids predicted from studies by Keys et al 1965a,b, Hegsted et al 1965, and Hayes et al 1991a,b. Figure adapted from Grundy (1981).

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 rapeseed oil (Canola). Until recently it was thought that MUFAs were neutral in relation to serum cholesterol lowering. The effects of MUFAs on serum cholesterol have been re-examined recently in a number of studies (Grundy 1986, Grundy et al 1988, Mattson and Grundy 1985, Mensink and Katan 1987). 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.

Polyunsaturated fatty acids (PUFAs)

There are two classes of PUFAs which occur in the diet, omega-6 (n-6) and omega-3 (n-3). The major dietary n-6 PUFA is linoleic acid (18:2 n-6). More highly unsaturated n-6 PUFAs such as arachidonic acid (20:4 n-6) can either be synthesised from linoleic acid or be obtained in small quantities from animal food sources. Although increasing linoleic acid will lower LDL cholesterol its effects are only half that of lowering dietary saturated fatty acids. The serum cholesterol lowering potential of linoleic acid is shown in figure 1.

The parent n-3 PUFA is alpha-linolenic acid (18:3 n-3). High levels of alpha-linolenic acid are found in some vegetable oils (soybean, rapeseed, linseed). The long chain n-3 highly PUFAs (eicosapentaenoic 20:5, docosapentaenoic 22:5, and docosahexaenoic acid 22:6) can either be synthesised from alpha-linolenic acid or obtained from the diet. Fish and fish oils are major sources of these fatty acids.

Fish oils consistently reduce serum triglyceride concentrations, particularly in hypertriglyceridaemic subjects (Harris et al 1983, Illingworth et al 1984, Nestel et al 1984). Although substitution of SFAs with n-3 PUFAs has been found to result in a fall in total cholesterol (Ahrens et al 1959, Keys et al 1957a) and LDL cholesterol, this effect seems to be due to reduced SFAs. Supplementation with n-3 PUFAs has been reported not to lower LDL cholesterol (Rogers et al 1986), and lowering of serum triglycerides with fish oils is often associated with an increase in LDL cholesterol (Connor 1986), particularly in association with diabetes (Van Dongen 1988).

Fish oils also affect the haemostatic system and eicosanoid metabolism. The overall result of an increase in the intake of n-3 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 n-3 fatty acids on cardiovascular disease may operate through the haemostatic system and eicosanoid metabolism rather than through lipoproteins.

Trans fatty acids

Trans fatty acids are generated during the process of hydrogenation of oils. A number of studies have examined

the relationship between trans fatty acids in the diet and serum lipoproteins. Many of these studies conducted during the 1960s produced inconsistent findings. In a recent well-designed study by Mensink and Katan (1990), it was found that trans fatty acids significantly reduced HDL cholesterol, increased LDL cholesterol significantly, and were at least as unfavourable on serum lipoproteins as SFAs. The Australian diet provides trans fatty acids in small quantities by way of margarine and other hydrogenated oils, as well as ruminant fat. Recent observations by Mensink et al (personal communication) indicate that trans fatty acids raise plasma Lp(a) and palm oil, rich in palmitic acid (16:0), either does not change, or lowers it.

Modification of other nutrient intakes and hyperlipidaemia

Carbohydrates

High carbohydrate diets reduce LDL cholesterol (Grundy et al 1988) 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 (MacDonald 1967). It must be kept in mind, however, that serum lipoproteins are not the most important outcome. Cardiovascular disease, and death are obviously more important. Although evidence from intervention trials examining carbohydrates specifically is limited, prospective studies have found inverse relationships between carbohydrate intake and CVD (Gordon et al 1981, Yano et al 1978).

Dietary fibre

Numerous studies have suggested that an increased consumption of fibre rich foods can reduce serum cholesterol levels (Anderson et al 1984, Jenkins et al 1979, Keys et al 1960). However not all dietary fibres appear to influence serum lipoproteins. Insoluble fibres (eg wheat bran) have little influence on serum lipoproteins (Jenkins et al 1986). 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 (LSRO 1987). Oat bran may also lower triglycerides in hypercholesterolaemic people (Anderson and Tietyen-Clarke 1986).

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 hyperlipidaemics (Descovich et al 1980, Goldberg et al 1982, Sirtori et al 1979, 1985). However, the effect is less consistent in normocholesterolaemic people (Bodwell et al 1980, Van Raaij et al 1979, Wolfe et al 1986).

Alcohol

Alcohol consumption produces an increase in serum triglyceride concentrations as a result of elevation of VLDL and chylomicron levels (Leiber et al 1963). There is also some elevation of serum cholesterol levels. A proportion of this is due to an increase in HDL cholesterol (Glueck et al 1981, Barrett-Conner and Suarez 1982). The rise in HDL cholesterol occurs only in inactive individuals, not in runners where HDL levels are already raised (Hartung et al 1983).

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 (Glueck et al 1986).

Micronutrients

There is no conclusive information on micronutrients and their effects on either serum lipoproteins or CVD mortality, although the MONICA study (Gey et al 1991) and a Scottish study (Riemersma et al 1991) look favourable for Vitamin E status. Early reports of an intervention study with beta-carotene (30mg alternate days in the US Physician study) are encouraging (MacLennan, personal communication). But similar doses (20mg daily) in the Australian Polyp Prevention Project (APPP) are associated with a greater recurrence of polyps at two years (MacLennan et al 1991). Niacin in doses used to lower serum cholesterol should be regarded as a pharmacological rather than a nutritional approach.

Non-nutrient food components

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 (Zock et al 1990), allicin from garlic (Kritchevsky 1991, Shao 1982). Saponins from foods like chick peas (Oakenfull 1990), tocotrienols from barley and palm oil, which appear to have HMG CoA reductase inhibitor activity (Qureshi 1991a,b); and plant sterols which may be handled alternatively to cholesterol (Tilvis and Miettinen 1986). With the growing evidence for physiological effects of phyto-estrogens in humans (Wilcox 1990) and serum cholesterol-lowering properties in experimental animals of certain natural food colours like anthocyanins (Igarashi and Inagaki 1991, Igarashi et al 1990), 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, 1–3 per cent lowering of LDL cholesterol, cumulatively, several components could be important.

Diet and cardiovascular disease

Dietary intervention studies examining end points other than serum lipoproteins have been relatively few in number. Cardiovascular end points which have been used in dietary intervention studies include: myocardial function, coronary atherosclerosis, myocardial infarction, CVD mortality, and total mortality.

Myocardial function

The evidence for a relationship between diet and myocardial energy metabolism comes from a study by Thuesen et al (1984). In this study it was found that a low fat diet, consisting of 10 per cent of energy from fat, improved the efficiency of energy usage by the myocardium in patients with angina. Coronary sinus blood flow and myocardial oxygen consumption were both reduced. These results indicate that in individuals with angina, a low fat diet may improve myocardial function. Further work is required to confirm these findings.

Coronary atherosclerosis

The influence of diet on the appearance of new lesions, detected angiographically, in human coronary arteries was examined by Blankenhorn et al (1990). Coronary angiograms from the subjects who received the placebo in the Cholesterol Lowering Atherosclerosis Study (CLAS), along with 24 hour dietary recall information were used to examine the relationship between change in diet and the appearance of new lesions. The placebo group were given dietary goals: to reduce total fat to less than 26 per cent (5 per cent SFAs, 10 per cent MUFAs and 10 per cent PUFAs). It was found in this study that increased intake of total fat, PUFAs, linoleic acid (18:2 n-6), oleic acid (18:1 n-9), and lauric acid (12:0), were associated with a significant increase in risk of new lesions. Increased protein intake was associated with a reduced risk of new lesions. The results in this study indicate that when total dietary fat and SFAs are reduced, the preferred substitutes may be protein and carbohydrate rather than PUFAs and MUFAs (Blankenhorn et al 1990). This study also showed an increased risk of new lesions with an increased intake of PUFAs and linoleic acid. This is in conflict with studies on dietary PUFAs and serum lipids which suggest a reduced risk with increased PUFA intake. They also conflict with cross-sectional data from Scotland (Wood et al 1984) and findings from results of a case-control study (Wood et al 1987) which found a beneficial relationship for linoleic acid. There are a number of possible explanations for the inconsistent finding, most of which relate to the suggestion that although it is important to have an adequate linoleic acid intake, a high intake may increase CAD risk; the difference in findings between Scotland and the USA may reflect this.

In another study with an angiographic end point by Ornish et al (1990), it was found that lifestyle changes including diet may be able to bring about regression of coronary atherosclerosis within one year. The dietary intervention in this study was a low fat vegetarian diet for one year. Dietary change, however was not the only lifestyle factor included in this study, and the effects of dietary change were therefore confounded by other lifestyle changes.

Cardiovascular disease events and mortality

Studies of diet as the only intervention, aiming for a reduction of cardiovascular mortality and/or incidence are presented in table 1. Few primary intervention trials have included changes in diet as the only intervention (Dayton et al 1968, Miettinen et al 1972). In the study by Dayton et al (1968), the effects were examined of two diets containing about 40 per cent 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 per cent of total fat intake, each of linoleic and oleic acid, reduced serum cholesterol by 12.7 per cent. The experimental diet was associated with a 31 per cent reduction in all atherosclerotic events. There was little difference in total mortality rates, however.

The second of the diet-only primary intervention studies was the Finnish Mental Hospital study (Miettinen et al 1972). 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 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.

The findings from these two studies were not conclusive due to the small number of subjects or the lack of appropriate controls. Large scale diet-only primary intervention studies have not been performed because of concerns about feasibility. Other diet-only 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.

In four large scale trials (the WHO Multifactorial Trial (WHO 1983); the Multiple Risk Factor Intervention Trial (MRFIT 1982); the Lipid Research Clinics Program (1984a, 1984b); and the Oslo study (Hjermann et al 1981)), reductions in total cholesterol of -1, -2, -9 and -13 per cent respectively were achieved. The differences in coronary rates were -4, -7, -19 per cent, and -47 per cent respectively. The degree to which diet alone may have contributed to these changes is unclear due to the confounding effects of other CVD risk factors. None of these studies reported a reduction in total mortality. But, the reduction in CVD risk was proportional to the degree and duration of cholesterol lowering achieved. A 1 per cent reduction in serum cholesterol was associated with a 2 per cent reduction in risk of CVD mortality. However, because of the order of individual variation in serum cholesterol, one cannot speak of a biologically meaningful decrease in serum cholesterol of only 1 per cent, but rather somewhat larger changes; unless, of course repeated measurement of replicates are made before and after intervention (Gordon et al 1987). A recent multifactorial primary intervention trial by Strandberg et al. (1991) has produced results which appear inconsistent with similar studies. It was found that after five years of intervention, and 11 years of follow up, the intervention group had a higher CVD mortality and total mortality when compared to the control group. These results have been difficult to explain.

Shekelle and Stamler (1989) have demonstrated the predictive power of dietary cholesterol independent of lipoprotein status, on CHD mortality, but we do not have a single factor cholesterol intervention study, nor are we likely to.

Several secondary intervention trials have been conducted (Table 1). Intervention in most of these studies involved either low fat or high P/S ratio, or both. Some of these studies have found that intervention produced a reduction in CVD mortality (Morrison 1955, Leren 1970, Bierenbaum et al 1973), however not all (Rose et al 1955, MRC 1965, Woodhill et al 1978). Perhaps one of the most interesting of these studies was published recently by Burr et al (1989). A significant reduction in total mortality was shown in a randomised controlled study (Burr et al 1989). This study examined the effects of dietary intervention on secondary prevention of myocardial infarction. Two thousand and thirty three men were allocated to receive advice or not to receive advice of three dietary factors: a reduction in fat intake with an increase in the PUFA to SFA ratio, increased fibre intake, or increased intake of fatty fish. It was found that the intake of fatty fish reduced two year all causes mortality by 29 per cent. No significant changes were found in the other two dietary interventions although questions of adherence to these interventions have been raised.

Foods and CVD

For all the effort to create a view of dietary management from intervention studies, it is necessary to draw on prospective studies of food intake, and coronary and total mortality to have a clinical approach in which we can be confident. These studies basically show that people who have a high plane of energy nutrition (Kushi et al 1985, Kromhout et al 1984, Lapidus et al 1986, Morris et al 1977), a high plant food intake (Kushi et al 1985), and a higher intake of fish (Kromhout et al 1985) have better survivals.

Epidemiological studies also point to the importance of the social function of food as a mediator of health effects; of educational status as interactive with food intake in decreasing coronary risk (Gill 1991); and of food indices (eg variety, traditionality) as being of value in predicting health outcomes (Wahlqvist et al 1991). Increasingly, mechanisms for these modus operandi of food on health, and cardiovascular disease in particular, are being appreciated.

In relation to lipoproteins, prevention of, and attention to obesity and abdominal fatness may be one of the most useful nutritional strategies to minimise lipoprotein abnormalities.

Where a reduction in **total fat intake** is achieved by a reduction in dietary **SFAs**, it is certainly favourable to lipoprotein status, and the evidence, although not strong at the present time, also suggests that it is favourable to coronary mortality.

All saturated fatty acids may not have equal effects on serum lipoproteins and coronary outcome. **Trans fatty acids** will probably need to be regarded as at least as detrimental to lipoproteins as SFAs. **Polyunsaturated fatty acids** have at least to be distinguished into the n-6 and n-3 series. Increased intake of the n-6 PUFAs has been shown to reduce serum cholesterol. However this may actually result in coronary lesion progression in those who already have adequate intake. Prudence may be required in this area of dietary change. For n-3 PUFAs , although triglycerides may be favourably affected, some patients, especially those with diabetes, may also experience an increase in LDL cholesterol. Substitution of SFAs with **MUFAs** has at least equivalent effects to a reduction in SFAs alone. This seems to be unrelated to the source of the oleic acid.

Several clinical trials where changes in saturated fats have been included have demonstrated reduced CVD mortality. However the intervention has rarely had a major impact.

Other macronutrients including **carbohydrates, fibre, proteins, and alcohol** can have significant effects on lipoprotein levels, although the effects of dietary intervention with these nutrients, on coronary mortality and total mortality is virtually unknown. There is however, growing evidence that a **plant food** orientation, and therefore a carbohydrate orientation, in the diet may favourably influence CVD. The evidence for an association between the various **micronutrients** and either plasma lipoprotein levels, or coronary and total mortality is limited.

Non-nutrient components of foods with small lipid lowering properties may be cumulatively important in an overall diet. Therefore even as far as lipoproteins are concerned, the total dietary approach may be more important than the single nutrient approach.

As far as **foods** are concerned, the only food specific intervention study available is with **fish**, which has been favourable for total mortality. It is difficult to envisage how food intervention without pattern change will be possible. In the mean time it is important to draw upon prospective studies of food intake in clinical decision making. These studies strongly support a plant food and fish orientation in the human diet to reduce coronary and total mortality. Food variety is particularly attractive as a candidate for such enquiry. It seems even more likely that, if an integrated dietary approach were used in an intervention study, favourable effects on total mortality might be seen. The design of such a study will require better knowledge of food composition and food habits than at present, and better ways of mathematically describing the total diet. However, we have reached the point where the classic Diet-Heart hypothesis requires a consideration of considerably more than dietary fat and more than serum lipoproteins as currently measured.

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