Dietary fats and coronary heart disease

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Summary – The prevention and treatment of coronary heart disease (CHD) necessitates vigorous dietary intervention so as to lower the serum cholesterol level by at least 6%. Greater decreases in serum cholesterol can bring about reversal of atherosclerosis. The critical dietary change is the reduction in intake of saturated fat and cholesterol. Some of this fat may be replaced by unsaturated fats, especially monounsaturated fat (olive or canola oil). Fish and the omega-3 fats they contain may also be useful for the prevention of CHD. The benefits of omega-3 fats occur within a few months and probably involve an anti-thrombotic effect. There is evidence that the intake of *trans*-fatty acids formed by the hydrogenation of oils should be reduced as they are associated with CHD. Hypolipidaemic drugs may be useful for persons at very high risk of CHD but should generally be avoided for primary prevention.

coronary heart disease / omega-3 fatty acids / trans fatty acids

INTRODUCTION

The story of dietary fat and coronary heart disease (CHD) covers the twentieth century. Yet, new chapters continue to be written. In this paper I will look at the role of different fats and discuss the most appropriate diet for the prevention and treatment of CHD.

BLOOD CHOLESTEROL, ATHEROSCLEROSIS AND CHD

There is now convincing evidence that an elevated blood cholesterol level plays a central role in CHD. (It may be mentioned that the key parameter is *blood* cholesterol; no one has ever died from an elevated *serum* cholesterol).

Law and colleagues recently reanalyzed the evidence concerning the relationship between blood cholesterol and the risk of CHD. They reported a much stronger relationship than that generally reported elsewhere. International studies indicate that in middle-age a 0.6 mmol/L lower serum cholesterol (about 10% of Western values) corresponds to a reduced risk of CHD death of 38% in men and 31% in women [29, 32]. In one study differences in serum cholesterol were reported to account for 80% of the ten-fold variation in CHD risk across 17 countries [30]. Similarly, prospective studies indicate that a 0.6 mmol/L lower serum cholesterol indicates a reduced risk of CHD of 54% at age 40, falling to 20% at age 70 [32].

There is convincing evidence that an elevated blood cholesterol level causes clinical CHD and that to a large extent this occurs by way of atherosclerosis. (The important role played by thrombosis as a mechanism by which high-fat diets cause clinical CHD will be considered later). The International Atherosclerosis Project examined 23,200 autopsied arteries from 14 countries [37]. An elevated serum cholesterol level was found to be a strong predictor of atherosclerosis [53]. Moreover, atherosclerosis was present to a more advanced degree in subjects with CHD [55].

Another approach that has been pioneered in recent years is the use of angiography so as to quantify the extent of atherosclerosis in living people. Angiograms of 723 men under the age of 40 admitted to the Cleveland Clinic (Cleveland, OH, USA) revealed that the extent of arterial closure steadily increased with the serum cholesterol level [62].

They are as sick that surfeit with too much as they that starve with nothing – Shakespeare, *Merchant of Venice*.

The above evidence leaves no doubt that a re-
duction in blood cholesterol is the key to both
the prevention and treatment of CHD. Moreover,
it is clear that the large majority of people in most
Western countries have a blood cholesterol level
that places them at risk of CHD.

Much controversy surrounds the question as to
the dividing line between normal and high serum
cholesterol level. Typically, this is placed around
6.2 to 7.0 mmol/L. In fact, strong evidence shows
that atherosclerosis does not develop when the
serum cholesterol is below 4.0 mmol/L but
steadily develops at higher levels [14, 48]. A level
of 5.0 mmol/L is clearly atherogenic, albeit con-
siderably less so than one of 6.0 mmol/L. This
was demonstrated by Keys and colleagues in the
1950s [26]. Men in Japan at that time had a diet
containing only 10% of energy as fat. Their serum
cholesterol was 3.9 mmol/L and few had severe
atherosclerosis, even when aged over 60. In con-
trast, Japanese men in California had adopted the
American diet and along with it, the American
levels of serum cholesterol and atherosclerosis.

THERAPY FOR CHD

The standard therapy for an elevated blood
cholesterol level is to reduce the intake of fat and
saturated fat, but only to a modest degree. For
instance, the step I diet advocates a maximum in-
take of fat and saturated fat of 30% and of 10%,
respectively. However, this causes a drop in
serum cholesterol of only about 2% [43, 44]. A
major reason for this is poor compliance. This ac-
counts for the failure seen in several trials to
successfully achieve a reduction in CHD. The
Multiple Risk Factor Intervention Trial (MRFIT)
[40] and the European Collaborative Trial [65]
achieved serum cholesterol reductions of under
3% and, not surprisingly, saw little change in
CHD prevalence.

Achieving a clinically significant impact on
CHD demands a statistically significant impact on
blood cholesterol. As pointed out by Temple and
Walker [56] those dietary trials that achieved a
serum cholesterol reduction of more than 6%
were mostly successful in reducing CHD rates.
This conclusion is supported by the results of
drug trials: pharmacological reduction of blood
cholesterol leads to a lowering of CHD rates
[33, 34, 36, 51].

Overall, the results of controlled trials indicate
that when the blood cholesterol is lowered,
whether by diet or drugs, it takes five years
before the full benefit becomes manifest. By that
time a 0.6 mmol/L reduction in serum cholesterol
translates to a 25% reduced risk of CHD [32].

An effective diet to achieve the requisite lower-
ing of blood cholesterol is one containing 20-30%
of energy as fat with saturated fat reduced to 5-
7%. It is important that some of the displaced fat
is replaced by foods rich in soluble fibre, such
as oats, beans and fruit. Such diets can lower the
cholesterol level from 6% to over 20%. Anderson
and colleagues [1] have for many years employed
such high-carbohydrate/high-fibre diets in therapy
not only for hyperlipidaemia but also for obesity
and diabetes.

This dietary strategy was tested, albeit in an
especially strict form, in the Lifestyle Heart Trial
conducted in San Francisco, California [42].
Patients with CHD were randomized to either an
intervention treatment (IT) group or to a usual
care (UC) control group. The IT were prescribed
a lifestyle programme that included a very low-fat
diet (under 10% of energy) with the elimination
of almost all foods of animal origin. The pro-
gramme also included moderate aerobic exercise,
stress management training, smoking cessation
and group support. The UC patients were asked
to follow a more conventional intervention diet
so as to reduce their fat intake to 30% of energy.

Changes in atherosclerotic lesions were assess-
ed by angiography conducted at baseline and after
one year. The average percentage diameter steno-
sis regressed from 40.0 to 37.8% in the IT group
but increased from 42.7 to 46.1% in the UC
group. Partial reversal (regression) of lesions was
documented in 82% of IT patients but in only
42% of UC patients. These changes reflect the
fall in serum cholesterol of 24% and 5% in the
IT and UC groups, respectively. It is particularly
noteworthy that progression of atherosclerosis
was observed in 53% of UC patients. This de-
monstrates that the standard therapy for CHD
does not heal the condition but, at best, merely
slows the rate at which it worsens.

Another important observation concerned the
frequency of angina; this fell by 90% in the IT
patients but rose by 165% in the UC patients. Im-
provements in angina were observed in only one
month. This suggests that a low-fat diet can im-
prove angina independent of changes in athero-
sclerosis.

A study in Heidelberg, Germany, also showed that a low-fat diet together with exercise could stop the progression of atherosclerosis [52]. Subjects living with stable angina received a fat modified diet (UC; fat reduced from 37% to 34% of energy; energy intake reduced by 19%) or a low-fat diet (IT; fat reduced from 40% to 26% of energy; energy reduced 27%). The serum cholesterol was unchanged in the UC group but fell by 10% in the IT group. Angiography demonstrated that after one year, fewer subjects in the IT group had progression (20% vs 42%) while more showed reversal (30% vs 4%).

The St Thomas Atheroma Regression Study (STARS) is also of importance as it was the first randomized, controlled trial to show that diet alone could reduce blood cholesterol sufficiently to open blocked coronary arteries [61]. Middle-aged men in London with CHD and a plasma cholesterol over 6.0 mmol/L received either usual care or a low-fat diet. (A third group received diet plus a hypolipidaemic drug but this group will not be considered further.) The modified diet reduced fat from 42% to 27% of energy and saturated fat from 17% to 9%, while soluble fibre was markedly increased.

After 39 months, the plasma cholesterol was unchanged in the UC group but was lowered by 14% in the IT group. Together with this the IT had an increase in the proportion showing reversal of artery narrowing from 4 to 38%. As in the Lifestyle Heart Trial the IT group had a marked fall in angina.

The demonstration that atherosclerosis is reversible is a discovery of profound importance. It indicates that with enough determination the fundamental problem causing CHD can be solved. In fact, this had been demonstrated in monkeys as long ago as 1970 [3].

THE ROLE OF UNSATURATED FATTY ACIDS

In many diet intervention trials saturated fat has been replaced by polyunsaturated fat. Quite apart from their hypocholesterolaemic affect, there is additional evidence indicating that these fats may be cardioprotective. Prospective and retrospective studies have revealed that tissue levels of linoleic acid, the most common polyunsaturated fatty acid, are lower in CHD cases than in controls [64]. Changes in national intake of polyunsatu-

rated fat appear to partly explain trends in CHD mortality rates: intake has climbed considerably in Australia and the United States where CHD mortality has fallen most [23].

In recent years the spotlight has turned on monounsaturated fats. The impetus for investigating such diets came from studies of the traditional Mediterranean diet. That diet is typically rich in olive oil and therefore mono-unsaturated fats. Keys et al [24] demonstrated in their Seven Countries Study, which was carried out in the 1950s and 1960s, that the Mediterranean countries have CHD mortality rates two- to three-fold lower than that found in northern Europe or the United States.

Further analysis revealed that across the 15 cohorts there is a correlation of 0.66 between the ratio of mono-unsaturated fat to saturated fats and the 15-year mortality rate for CHD [25]. When this was adjusted for entry values of age, body mass index, blood pressure, and number of cigarettes smoked, the correlation then climbed to 0.98. This accounts for a remarkable 96% of the variance in CHD mortality. In other words, these data indicate that CHD may be greatly reduced by minimizing the intake of animal fats (and therefore saturated fat) and replacing them with olive oil.

For many years it was believed that mono-unsaturated fats were neutral as regards the serum cholesterol. However, more recent evidence indicates that they are as effective as polyunsaturated fats at lowering the serum cholesterol [38].

Rivellese et al [46] fed diets rich in mono-unsaturated fats to hyperlipidaemic subjects in Italy. The diets contained either 27% fat, 17% mono-unsaturated and 4% polyunsaturated, or 36%, 19% and 10%, respectively. Both diets contained only 6-7% saturated fat. Each diet reduced plasma cholesterol by about 9%. This indicates that provided the intake of saturated fat is reduced, cholesterol control can be achieved with diets rich in mono-unsatured fat.

Garg et al [16] compared two diets in patients with type II diabetes. The first was a low fat diet (30% of energy as fat) and the second contained 45% of energy as fat, much of it being from mono-unsaturated fat. No differences were seen in plasma cholesterol, LDL-cholesterol or HDL-cholesterol. However, the low-fat diet caused a raised plasma level of glucose, insulin and triglyceride which persisted at 14 weeks. This indicates that an increased intake of mono-unsaturated fat can

lower the level of blood cholesterol while avoiding the raised levels of triglyceride, glucose and insulin that may occur with a low-fat diet, especially in diabetics.

These observations suggest that provided the intake of saturated fat is sharply reduced, the content of mono-unsaturated fat may thus be liberalized. However, other evidence suggests that we should be cautious before adopting that view. First, Anderson et al [1, 2] investigated and reviewed the effects of high-carbohydrate diets, particularly in diabetics. They assert that provided the fibre intake is high, such diets are thus not only effective at lowering the blood cholesterol but also help achieve glycaemic control. Second, dietary fat is a major cause of obesity and is associated with various types of cancer [57]. Third, international studies show that the Western diseases – including CHD, obesity and type II diabetes – are rare in those societies where the diet is rich in carbohydrate and fibre, and low in fat [8, 60].

An increase in the intake of mono-unsaturated fat, either from olive oil or canola oil, would likely increase the acceptability of the diet. Surprisingly, however, subjects in the above Italian trial preferred the diet with the lower fat content despite living in a region where olive oil intake is traditionally high [46]. In the Lifestyle Heart Trial, also, adherence to and acceptability of a vegetarian, low-fat diet among cardiac patients was found to be quite high [7].

The first priority, both for primary and secondary prevention, must be to introduce a diet with a much reduced intake of saturated fat and cholesterol. By necessity this means that foods of animal origin should be eaten sparingly. At the same time the intake of foods rich in carbohydrate and fibre, especially fruit and vegetables, needs to be given much more prominence. If acceptability of the diet becomes a problem and people desire more fat in their diet, then olive or canola oil are appropriate choices.

OMEGA-3 FATTY ACIDS

Studies on Greenland Inuit (Eskimos) living on their traditional diets revealed a high intake of omega-3 fats, a prolonged bleeding time and a low risk of CHD [6]. These observations led to the discovery of the role of long-chain omega-3 fats, particularly eicosapentaenoic acid (EPA) and

docosahexaenoic acid (DHA), as a preventive of thrombosis.

Supplements of fish oil alter the composition of the platelet membrane and the balance of prostaglandin metabolism [49]. As a result the clotting time is slowed and thrombosis is less likely. The dose of fish oil required to exert a significant lengthening of the clotting time is about 3-5 grams per day, making this impracticable as an anti-thrombotic agent for the general population.

However, there is evidence that fish may be a preventive of CHD at relatively low intakes. The Zutphen Study, a prospective study in the Netherlands, revealed that small amounts of fish are protective against CHD mortality [27]. In this study the protection was clearly seen for both fatty fish and for non-fatty fish. Other studies have also reported that fish or EPA is protective [9, 28]. In the Multiple Risk Factor Intervention Trial, a nested case-control study, the serum level of omega-3 fatty acids was negatively related to risk of CHD [54].

In contrast to these observations, two large prospective studies in the United States published in 1995 did not observe a protective relationship between the intake of fish or omega-3 fats and risk of CHD [5, 39]. One of these studies also reported no relationship between plasma levels of long-chain omega-3 fats and myocardial infarction [39]. These negative results do not necessarily cast doubt on the value of fish or omega-3 fats; it should be remembered that prospective studies have also failed to document a direct association between the intake of saturated fats and CHD.

These results are suggestive that fish and the long-chain omega-3 fats they contain may be protective against CHD. This possibility was tested in the following clinical trial. CHD patients recovering from a myocardial infarction were instructed to consume two portions of fatty fish per week, amounting to at least 300 grams [10]. Patients unable to eat sufficient amounts were given fish oil capsules as a partial or total substitute. The dietary intervention reduced CHD deaths by one-third. Non-fatal CHD, however, was not reduced.

One other trial pertinent to omega-3 fats will also be discussed as it produced especially exciting results. The Seven Countries Study had revealed exceptionally low rates of CHD in the Greek island of Crete [24]. Renaud, de Lorgeril and colleagues [13, 45] conducted a clinical trial in Lyon, France, using an intervention diet based

on the Cretan diet of the 1960s, a diet that was rich in legumes, fruit, fats (mostly olive oil) but had little meat.

Subjects recovering from myocardial infarction were randomized into two groups. The IT group was instructed to eat more bread, vegetables, legumes, fish and fruit but less meat and no butter or cream. Subjects received a special margarine made from canola oil. This resembles olive oil but has a higher content of omega-3 fats. The subjects were also instructed to use olive oil or canola oil as the only oil for salads and food preparation.

Compared with UC patients those in the IT group consumed one-third less saturated fats (8.3% vs 11.8% of energy), 24% more oleic acid (mono-unsaturated fat; 12.9% vs 10.4%), one-third less linoleic acid (the major omega-6 poly-unsaturated fat; 3.6% vs 5.4%) but 2.5 times more omega-3 fat (0.89 vs 0.35%).

After 27 months of follow-up, all forms of cardiovascular disease, including fatal and non-fatal CHD as well as stroke, were all reduced by 70-80%. Total mortality fell similarly. The components of the diet responsible for these highly impressive results are a matter of conjecture. As the beneficial impact of the diet was seen within a few months and serum lipid values were similar in the two groups, the mechanism is unlikely to involve reversal of atherosclerosis. This observation was also made in the previous trial. The most plausible explanation is that omega-3 fats greatly reduce the risk of thrombosis. The authors speculate that other factors that may be relevant are the lower intake of saturated fats, the higher intake of mono-unsaturated fat, the higher ratio of omega-3 to omega-6 fats, and the higher intake of anti-oxidant nutrients.

These two clinical trials have shown highly impressive results by incorporating sources of omega-3 fats into the diet. There is an urgent need for further research into this.

THE PROBLEM OF *TRANS* FATTY ACIDS

Trans fatty acids are formed when oils are hydrogenated so as to harden them and reduce the rate of spoilage by oxidation. As the following evidence indicates, these fats may increase the risk of CHD.

Trans fats have been shown to increase the serum level of total and LDL cholesterol [22, 35].

However, Nicolosi and Dietschy [41] have argued that this is only in relation to oleic and linoleic acids and that their effect should more accurately be classed as neutral. *Trans* fats may also lower the HDL cholesterol level and have other actions that increase the risk of CHD.

Several studies have revealed that persons with an increased intake of *trans* fats or an increased adipose tissue level are at a raised risk of CHD [63]. Intake of margarine, the chief source of *trans* fats, has been associated with risk of CHD in both a case-control study in Greece [59] and in a prospective study done as part of the Framingham Study [18]. Two recent studies, however, produced essentially negative results concerning the relationship between the *trans* fat content of adipose tissue and risk of CHD [4, 47]. However, in one of these studies, based on samples from eight European countries and Israel, there was a relationship between the level of C18:1 *trans* fatty acid and CHD when the data from Spain were excluded [4].

Bearing in mind that the intake of *trans* fats can be greatly reduced with minimal inconvenience (eg, by using non-hydrogenated margarine), it would appear wise to advocate a reduced usage of these fats.

DRUG THERAPY FOR HYPOLIPIDAEMIA

An alternative approach to the management of elevated cholesterol levels has been the use of hypolipidaemic drugs. Recently, there has been controversy concerning an excess of non-CHD deaths associated with these drugs. Smith et al [12] re-examined the results from drug trials and concluded that drugs lead to an excess of non-CHD deaths which may exceed the numbers of CHD deaths prevented. Clearly, if this is the case, then there is little point in using such drugs. With patients with an elevated serum cholesterol plus existing CHD (ie, secondary prevention) the risk of CHD death is likely to be so high that the reduced numbers of CHD deaths leads to a net gain. However, with patients with an elevated serum cholesterol but without existing CHD – the majority of potential patients – there is the possibility that drugs may actually kill more people than they save.

Law et al [31] analyzed the same data and concluded that hypolipidaemic drugs do not cause an excess of non-CHD deaths, except in the case of

clofibrate. Nevertheless, they conclude that "....cholesterol lowering drugs should not be used in response to mass cholesterol testing but that they may be used in patients with (CHD)".

Clearly, more evidence is needed before we can properly identify the patients for whom the benefits of hypolipidaemic drugs will exceed the risks. Certainly, a patient at exceptionally high risk of CHD and who has failed to control his blood cholesterol by diet should be given these drugs. A typical person in this class is a man with a serum cholesterol of over 7 mmol/L plus clinically evident CHD. However, the majority of patients currently being prescribed such drugs are at a much lower risk (eg, a man with a serum cholesterol of 6-6.5 mmol/L and who smokes but without clinically evident CHD). In such cases prudence would dictate that discretion is the better part of valor. A more appropriate intervention is to put much greater emphasis on dietary intervention.

AN OVERALL STRATEGY

Based on the evidence discussed here, the most important feature of an anti-CHD diet is the reduction of blood cholesterol levels by sharply reducing the intake of saturated fat and cholesterol. For a person who already has clinical CHD, this means reducing fat to about 20-25% of energy and saturated fat to about 6% of energy. In practice, that translates to a near-vegetarian diet. For the primary prevention of CHD this diet can be liberalized but should certainly have well under 30% of energy as fat and less than 8% of energy as saturated fat. This means that meat should be lean and eaten in modest amounts at most. Similarly, only low-fat milk should be used.

The partial replacement of saturated fats by unsaturated fats, particularly mono-unsaturated fat, is acceptable. However, the necessity for weight control must be borne in mind. Sources of omega-3 fats, namely fatty fish and canola oil, appear to be especially valuable but confirmatory evidence is required. Fish is certainly far preferable to meat. The use of these foods means that the diet need not be overly restrictive.

Hypolipidaemic drugs have a useful role but should, as far as possible, be reserved for patients at especially high risk. Diet and lifestyle change must be accorded top priority. However, as the results emerge from newer drugs, their use may

then become appropriate for more and more people.

Two other aspects of the diet should not be neglected. First, the diet should contain generous amounts of fruit and vegetables. These supply anti-oxidant nutrients which appear to play a valuable protective role against CHD [17]. Second, the intake of salt needs to be greatly reduced. This is a cheap, safe and effective way to decrease the risk of CHD and stroke [27]. In fact, there is probably no other diet or lifestyle change that can more easily reduce the risk of these two diseases.

These dietary changes should be considered part of a lifestyle approach to the prevention and treatment of CHD. As an integral part of this it is esential to target smoking and lack of exercise.

Studies of vegetarians provide compelling evidence for the benefits of a lifestyle approach. Comparative studies indicate that vegetarians have a lower (more favourable) body weight, blood pressure and serum cholesterol [50]. An eleven-year prospective study of German vegetarians revealed that compared with the German average the mortality rate was reduced by half for moderate vegetarians and by three-quarters for strict vegetarians. Cancer and stroke were also substantially reduced. All cause mortality was reduced by about half. Similar findings have been made in Britain [58]. These low rates of CHD and other diseases reflect not only a vegetarian diet but a generally healthier lifestyle. For instance, few of the German vegetarians were smokers. Perhaps the one clear conclusion is that a healthy *lifestyle* leads to greatly reduced disease and mortality rates.

One of the clear advantages of the treatment approaches described in this paper is that it carries a much reduced cost. This is particularly important when we bear in mind that health-care budgets in many countries are under severe pressure. Gould [19] estimated the cost of various forms of treatment for CHD (using American figures based on five years of treatment). Non-invasive treatment costs $8,000 plus a further $6,000 for drugs. In comparison, angioplasty costs $35,000 while bypass surgery costs $60,000.

The dietary changes advocated in this paper may be ideal but they are unlikely to be acceptable to the majority of symptom-free people. Indeed, most of the studies where major changes in diet or other aspects of lifestyle have been introduced have been on patients who al-

ready have CHD. For such people compliance is quite high.

Another group who might be expected to find lifestyle change acceptable are persons at high risk of CHD. Certainly, such people should be given every encouragement to reduce their risk of CHD. However, targeting this group has two serious limitations. First, it will only tackle a minority of future cases of CHD: Rose [49] pointed out that the 15% of men at high risk of CHD account for only 32% of future cases. Second, even subjects with major risk factors for CHD seem to be reluctant to change their lifestyle. This was shown in two recent British studies of health promotion in general practice; a poor response rate was achieved when patients were given detailed instruction on dietary and other lifestyle changes [15, 20, 21].

If the war against CHD is to be won, this will not occur in the physician's office. Rather, it will take place at the population level. A new and fast developing quasi-medical field is health promotion. This investigates the social, economic, political and organizational sources of disease and proposes appropriate policies. For instance, in a forthcoming book I argue that there is an urgent need for action at the government level to improve people's lifestyles. This includes the use of taxes and subsidies so as to shift food consumption patterns towards healthier foods (Temple, submitted for publication). At present national food policies in most countries are dominated by questions of economics rather than health.

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