Dietary fats in the prevention of coronary heart disease: the need for more clinical trials

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On the basis of various lines of evidence, including clinical trials, diet appears to have the potential to lessen the risk of CHD events, independent of effects on serum lipid values, at least as great as the most effective medical and interventional treatments available today. Given the diversity of these cardioprotective diets, as well as their salutary components, one of the priorities in research should be to undertake more comparative trials, trials which determine patient acceptability, effects on surrogate markers of risk, and which ultimately impact on morbidity and mortality.

The Carolina Diet Heart Trial is a clinical outcome trial comparing two 'proven' cardioprotective diets, the AHA endorsed Step II diet versus an American–Mediterranean diet, and having the amount and type of unsaturated fat as the main dependent variable. This study is a prospective, randomized, multi-centre, secondary prevention trial with the ultimate intention of reducing the incidence of subsequent cardiovascular events through dietary modification in patients who have survived a previous acute coronary syndrome. The study intervention is also designed to give these patients the necessary knowledge, motivation and practical ability to modify their current diets and maintain long-term adherence to a more cardioprotective diet. The initial pilot phase will assess compliance with the two study diets, as well as assess the impact of each diet on a marker of CHD risk.

Key Words: n-3 fats, Mediterranean diet, whole dietary pattern.

Introduction

The best diet for the prevention of coronary heart disease (CHD) is unknown. Supported by animal experiments and large cohort studies, clinical outcome dietary trials have basically established that restricting saturated fat intake while substituting polyunsaturated fats will lower the risk of CHD roughly proportional to the degree of serum cholesterol lowering\cite{1,2}. This data forms the basis of the American Heart Association (AHA) and European recommendations for diet in secondary prevention, which are nearly identical and summarized by restrictions in fat intake: total fat <30% of total calories, saturated fat <7%, and cholesterol <200 mg·day\(^{-1}\)\cite{3,4}. There are two main reasons, however, why this approach to the dietary prevention of CHD may no longer be valid.

First, statin therapy is far more powerful in both cholesterol-lowering effectiveness and in reduction of CHD morbidity and mortality\cite{5,6,7}. All of the clinical outcome trials establishing the clinical effectiveness of saturated fat restriction with polyunsaturated fat substitution were conducted long before the era of statins, as were other highly effective pharmacological therapies used in prevention\cite{8–10}. There is no evidence that any additional benefit is derived by adhering to such a diet in this context. Two more recent multi-interventional trials have shown that the combination of a low-fat, high-carbohydrate diet plus modification of traditional risk factors (e.g. hypertension, smoking, etc.) reduces angiographic progression of coronary disease and hospital admission for coronary events, but it is impossible to distinguish the contribution of the dietary changes to this success\cite{11,12}.

Secondly, ever since early ecological observations revealed that certain ethnic populations have very low rates of CHD in spite of relatively high fat consumption\cite{13,14}, evidence has been accumulating that some diets are cardioprotective independent of a major effect on serum cholesterol. Three clinical trials have been undertaken in recent years which have tested whether presumed cardioprotective diets can reduce the risk of cardiac events in populations with known CHD.

Cardioprotective diet trials

The first of these was the Diet and Reinfarction Trial (DART), which compared three diets: a low saturated fat diet plus increased polyunsaturated fats, a high fish
diet (requiring at least two portions of fatty fish or fish oil supplements per week), and a high-fibre diet. Only the group given fish advice had a significant reduction in CHD deaths; overall mortality was reduced 29% after 2 years, although there was a non-significant increase in myocardial infarction rates. Nevertheless, these studies lay the foundation for further studies of cardioprotective nutrient combinations are critical, and what dietary changes are most beneficial, whether certain foods or food groups alone or in combination. Evidence that the benefit of these cardioprotective diets derives primarily from the increase in n-3 fatty acid consumption. For example, in the Lyon Diet Heart Study, the experimental diet group consumed less total fat (30.5% versus 32.7% of total calories), less saturated fat (8.3% versus 11.7%), less cholesterol (217 mg/day versus 318 mg/day), less linoleic acid (3.6% versus 5.3%), more alpha-linolenic acid (0.81% versus 0.27%), and more oleic acid (12.9% versus 10.3%). Diets in the Indian and Lyon trials were also characterized by higher intakes of fresh fruits, vegetables, legumes and cereals, which increased the amount of whole-grain, fibre, natural antioxidants (e.g., polyphenols such as flavonoids), minerals, arginine (an amino acid with major effects on vascular and platelet function), vitamins. Support for the cardioprotective benefits of these ‘other’ ingredients comes from numerous recent observational trials, which have indicated strong inverse associations between CHD incidence and consumption of whole-grain, fibre, nuts, fruits and vegetables, folate, vitamin B6, and flavonoids. The effect of a similar low-fat whole dietary pattern was recently assessed in a large cohort study using a ‘recommended food score’. This score was based on how often an individual ate foods from a list of fruits, vegetables, whole grains, low-fat milk and lean meats and poultry. No foods high in n-3 fatty acids were included in the calculation. Those women in the highest quartile compared with those in the lowest had a relative risk of CHD of 0.67, a relative risk of cancer of 0.60, and an all-cause mortality relative risk of 0.69 over a median follow-up period of 5.6 years.

**Fish, fish oils and n-3 fatty acids**

Unlike the Indian and Lyon trials, the dietary intervention in DART was mono-factorial, namely higher fish/fish oil intake. Some[21–23] but not all[22–24], of the epidemiological studies addressing this question show an inverse correlation between CHD mortality and fish consumption. One explanation offered for this discrepancy is the variable baseline fish intake of the populations studied, with greater benefit derived for those groups with little to no regular fish consumption. The recently published GISSI–Prevenzione trial investigated the effects of fish oil capsules (providing approximately 850 mg of EPA plus DHA) in patients with recent myocardial infarction. This supplementation resulted in a 15% reduction in the combined end-point of death, non-fatal MI and non-fatal stroke, and a 20% reduction in total mortality after 3–5 years[25]. Sudden cardiac death specifically was reduced by 45% in the fish oil supplemented group. The latter effect is supported by various experimental studies in animals which have shown an antiarrhythmic effect of n-3 fatty acids[26,27]. Baseline fish consumption was quite high in all groups.

In the Lyon Diet Heart Study the authors propose that the most critical nutrient component was the higher intake of alpha-linolenic acid in the experimental group. Several large observational studies support this contention, having revealed a strong inverse association for alpha-linolenic acid and CHD mortality[28–30]. Nevertheless, it cannot be assumed without further evidence that the benefit of these cardioprotective diets derives primarily from the increase in n-3 fatty acid consumption. For example, in the Lyon Diet Heart Study, the experimental diet group consumed less total fat (30.5% versus 32.7% of total calories), less saturated fat (8.3% versus 11.7%), less cholesterol (217 mg/day versus 318 mg/day), less linoleic acid (3.6% versus 5.3%), more alpha-linolenic acid (0.81% versus 0.27%), and more oleic acid (12.9% versus 10.3%). Diets in the Indian and Lyon trials were also characterized by higher intakes of fresh fruits, vegetables, legumes and cereals, which increased the amount of whole-grain, fibre, natural antioxidants (e.g., polyphenols such as flavonoids), minerals, arginine (an amino acid with major effects on vascular and platelet function), vitamins. Support for the cardioprotective benefits of these ‘other’ ingredients comes from numerous recent observational trials, which have indicated strong inverse associations between CHD incidence and consumption of whole-grain, fibre, nuts, fruits and vegetables, folate, vitamin B6, and flavonoids. The effect of a similar low-fat whole dietary pattern was recently assessed in a large cohort study using a ‘recommended food score’. This score was based on how often an individual ate foods from a list of fruits, vegetables, whole grains, low-fat milk and lean meats and poultry. No foods high in n-3 fatty acids were included in the calculation. Those women in the highest quartile compared with those in the lowest had a relative risk of CHD of 0.67, a relative risk of cancer of 0.60, and an all-cause mortality relative risk of 0.69 over a median follow-up period of 5.6 years.

**Future dietary trials**

This brief overview highlights the fact that various constituents in diet are detrimental and even more are protective, in regard to coronary heart disease, but that most of these associations have not been tested in clinical outcome trials. It is certainly not feasible to study each component in separate intervention trials, nor would it necessarily provide accurate or practical information, since nutrients are consumed as part of a whole diet and may be dependent upon one another in having their most salutary effects. Therefore, whole dietary patterns which already have some evidence for...
being cardioprotective need to continue to be compared in metabolic studies and clinical trials. Specific issues, such as the clinical benefits of n-3 fats, must still be addressed in such whole-diet trials, while leaving the precise mechanism questions to be resolved in the laboratory. Studying different populations is essential as this variable may corroborate, or confound, results. For example, replicating the Lyon trial in the U.S.A. (or the U.K., northern Europe or Australia), would inevitably entail differences in the Mediterranean diet compared with southern France. However, comparable results would confirm the importance of the quantitative component of the nutrients being studied, while null results would highlight the importance of the qualitative differences, among other variables.

**An American–Mediterranean dietary trial**

In the U.S.A. the AHA and National Cholesterol Education Program Step II guidelines for fat intake have served as the starting point for recommendations made by physicians and dieticians to CHD patients for years (see the Introduction of this article). Most dieticians are providing further advice supported by nutritional research regarding the detrimental and cardioprotective effects of other nutrients (e.g. trans fatty acids, whole-grain, fibre, fish, fruit and vegetables). Many are presenting a ‘hybrid’ diet, trying to incorporate information on the benefits of n-3 fats and possibly monounsaturated fats, while restricting total fat in line with AHA guidelines, sometimes resulting in specific dietary recommendations that are incompatible. Some are ‘tailoring’ their advice according to the lipid profiles of patients. All of these approaches are understandable, but the confusion and lack of consistency is lamentable, and only weakens confidence and compliance with any advice. The solution is a clinical outcomes trial comparing two ‘proven’ cardioprotective diets, the AHA endorsed Step II diet versus an American–Mediterranean diet, with the main dependent variable being the amount and type of unsaturated fat. Even null results would allay patient and clinician anxieties and confusion over how much and which fats to recommend.

Clinical outcome trials, superior as they are in the hierarchy of evidence, are difficult and expensive. Before an adequate one could be conducted, a pilot trial would be necessary to prove feasibility, specifically that an American population can maintain long-term adherence to both diets. Knowledge, beliefs, cost, convenience and palatability are obvious issues to be addressed in achieving the necessary dietary changes; any difference in compliance would nonetheless help to determine which of these factors are most important and provide information useful in advising individual patients.

A pilot study could also further support the biological plausibility of a major clinical benefit from diet if reliable, strong surrogate markers of risk were positively impacted. As already mentioned, the cardioprotective dietary trials with the most dramatic reduction in CHD events had no significant impact on serum lipid values. Therefore, the primary mechanism of such a powerful effect remains speculative, even if it were determined to be related to the n-3 fat intake. Atherosclerosis, however, is more than a dislipidaemia aberration. Accumulating evidence suggests it is also an inflammatory disease. Given that n-3 fatty acids have potent anti-inflammatory properties, a reasonable hypothesis is that the success achieved in the Lyon trial was due to this mechanism. One of the best markers of inflammation, C-reactive protein, is also currently one of the strongest and most reliable markers of CHD risk. C-reactive protein therefore would be an ideal surrogate marker in a Mediterranean (high n-3 fatty acid) dietary trial. I have outlined what I think would be the necessary steps in making further progress toward understanding the role of diet in general, and n-3 fats in particular, in the prevention of CHD. We, at Carolinas Medical Center, have started taking these steps with a pilot trial, and hope to lay the foundation for a subsequent clinical outcomes trial.

**The Carolina diet heart study**

**Study design**

This study is a prospective, randomized, multicentre, secondary prevention trial with the ultimate intention of reducing the incidence of subsequent cardiovascular events through dietary modification in patients who have survived a previous acute coronary syndrome. The study intervention is also designed to give these patients the necessary knowledge, motivation, and practical ability to modify their current diets and maintain long-term adherence to a more cardioprotective diet. The initial pilot phase will assess compliance to the two study diets, as well as assess impact of each diet on a marker of CHD risk.

**Population and duration**

The pilot trial will enrol 144 patients of either sex, recruited from the participating cardiac rehabilitation centres over approximately 6 months. Patients will be followed for at least 6 months, for a total trial duration of 12 months.

**Inclusion criterion**

All patients must be 35–75 years old, and have a history of an acute coronary syndrome (myocardial infarction or unstable angina) or revascularization within 3 months of enrolment. They also must have the physical and mental ability to participate in a comprehensive cardiac rehabilitation programme, as judged by the referring
physician, the medical director of the programme, and by standard pre-entry criteria of the particular cardiac rehabilitation programme (e.g. exercise testing, ambulatory EKG monitoring).

Exclusion criteria

Criteria for exclusion include not meeting eligibility criteria for participation in the cardiac rehabilitation programme, uncontrolled hypertension (systolic >160 mmHg, diastolic >100 mmHg), or an inability to perform an exercise test due to recurrent angina, ventricular arrhythmia or high-grade AV block, or evidence of an unstable condition manifested during exercise testing (e.g. hypotension, syncope, severe ischaemic EKG changes).

Recruitment and enrolment

Consecutive patients who have survived an acute coronary syndrome in the previous 3 months and who are starting one of the participating cardiac rehabilitation programmes will be invited to participate by agreeing to be randomized to one of two diets. Both diets will be explained verbally and in written format in the informed consent. Patients will then be given 1–2 weeks to decide before their first appointment with the dietician. Each study site will have one dietician teaching both of the diets being compared in this trial in order to avoid the differential impact of the dieticians own personality and teaching success in achieving dietary compliance.

Diet intervention

Each patient (with spouse or other similar person instrumental in food selection) will attend an initial session with the dietician to receive detailed instructions in how to adhere to their particular diet. The specific content of the two diets is given in Table 1 (with designated differences shown with an asterisk): In order to decrease the n-6/n-3 ratio in the Mediterranean group, consumption of foods naturally high (or fortified) in n-3 fatty acids (e.g. fatty fish, canola-oil-based spreads, flaxseed oil and flour, n-3 fortified eggs, walnuts), will be specifically advised, and ongoing assistance provided in how to incorporate these foods into the diet. Fatty fish will be advised at least twice weekly. A canola-oil-based margarine will be recommended to these patients as well. To increase the monounsaturated fat intake, olive and canola oils exclusively will be recommended for salads and food preparation, and nut consumption 1/2–1 oz/day will be advised.

Compared with the average American diet, both groups will receive education and instruction in using:

more—
whole-grain and fibre (e.g. whole grain breads and cereals, at least two servings per day);
fruits and vegetables (five to nine portions combined per day), and;

less—
saturated fat (<7% of total daily calories);
trans fatty acids (<1·3% of total daily calories);
cholesterol and total fat (though the Mediterranean group will have a slightly higher allowance in order to accommodate the increased consumption of foods higher in n-3 and monounsaturated fats).

This verbal instruction will be reinforced with written material given to the patient at the time of their initial meeting with the dietician.

After the initial dietary instruction, adherence to the diets will be supported by:

(1) a follow-up visit with the dietician individually at 8 weeks to address individual problems with adherence.

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**Table 1 Specific contents of Step II and Mediterranean diets in the Carolina Diet Heart Trial**

<table>
<thead>
<tr>
<th></th>
<th>Step II</th>
<th>Mediterranean</th>
<th>AAD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fat (% of total calories)*</td>
<td>30%</td>
<td>34%</td>
<td>34%</td>
</tr>
<tr>
<td>Saturated (% total calories)</td>
<td>&lt;7%</td>
<td>&lt;7%</td>
<td>16%</td>
</tr>
<tr>
<td>Polyunsaturated (% total calories)</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td>7%</td>
</tr>
<tr>
<td>n-6/n-3 ratio*</td>
<td>na</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Alpha-linolenic acid (g. day⁻¹)*</td>
<td>na</td>
<td>≥ 2 g</td>
<td>1·2 g</td>
</tr>
<tr>
<td>EPA+DHA (mg. day⁻¹)*</td>
<td>na</td>
<td>≥ 650 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Monounsaturated (% total calories)*</td>
<td>10-15%</td>
<td>10-20%</td>
<td>11%</td>
</tr>
<tr>
<td>Trans fatty acids (% total calories)</td>
<td>&lt;1·3%</td>
<td>&lt;1·3%</td>
<td>2·6%</td>
</tr>
<tr>
<td>Cholesterol (mg. day⁻¹)*</td>
<td>&lt;200 mg</td>
<td>&lt;300 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Carbohydrate (% total calories)</td>
<td>≥ 50%</td>
<td>≥ 45%</td>
<td>50%</td>
</tr>
<tr>
<td>Protein (% total calories)</td>
<td>10–20%</td>
<td>10–20%</td>
<td>16%</td>
</tr>
<tr>
<td>Fibre (g. day⁻¹)</td>
<td>20–35 g</td>
<td>20–35 g</td>
<td>15 g</td>
</tr>
<tr>
<td>Total calories</td>
<td>To achieve and maintain desirable body weight</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Designated differences.
†AAD=average American diet for comparison purposes.
revealed on the food-frequency questionnaire at 6 weeks; (2) bi-monthly newsletters, consisting of practical, educational, and motivational material designed to enhance compliance; (3) educational group meetings three times in the first year, each consisting of recipe tasting, an educational lecture with question and answer session and group sharing.

Data collection

Demographic and baseline characteristics will be obtained consisting of age, sex, marital status, smoking history, infarction history, other medical diagnoses (including diabetes mellitus, hypertension, heart failure, atrial fibrillation and stroke history), surgical history (including coronary artery bypass grafting and angioplasty procedures), all medications (including vitamins and herbs) and family history of premature CHD. Weight, body mass index (BMI), blood pressure, and fasting lipid profile will be obtained at baseline and again at 6 months. Baseline dietary habits will be assessed by administration of a food-frequency questionnaire (the Harvard 96GP) at entry into the study.

Compliance with the study diets will be determined by the same food-frequency questionnaire at 6 months, and by RBC membrane fatty acid analysis obtained at baseline and 6 months.

Clinical event information will be ascertained from patients at all office visits, and by return of a self-addressed postcard enclosed in the bimonthly newsletters, which will be followed up with a phone call.

Outcome assessment

The primary end-points of the pilot trial are the mean intakes and the percentage of patients achieving the goal intake in each designated food or nutrient category (e.g. total fat, whole-grain, fibre, alpha-linolenic acid, EPA+DHA, n-6/n-3 ratio).

The primary clinical end-points are cardiac death, non-fatal myocardial infarction and total mortality. Secondary clinical end-points are unstable angina, heart failure, stroke, pulmonary or peripheral embolism, and revascularization procedures. Documentiation will come from hospital discharge summaries or death certificates. Validation of clinical events will be assured by an ad hoc committee of cardiologists or neurologists blinded to the patients’ dietary assignment.

Summary

On the basis of various lines of evidence, including clinical trials, diet appears to have a potential to lessen the risk of CHD events, independent of effects on serum lipid values, at least as great as the most effective medical and interventional treatments available today. Given the diversity of these cardioprotective diets, as well as their salutary components, one of the priorities in research should be to undertake more comparative trials, trials which determine patient acceptability, effects on surrogate markers of risk, and which ultimately impact on morbidity and mortality.

References