relation between smoking per se and atherosclerosis. In the seven-country study there was no significant association between CHD incidence and smoking in the different countries, and in the prospective necropsy series of the Oslo study a significant correlation between prevalence of coronary raised atherosclerotic lesions and smoking could not be shown.23,24

On the other hand it is possible that smoking intervention might be effective only when tobacco consumption is reduced to zero. This point may be relevant to our study, because most of the participants reduced their consumption but did not stop totally.

If this had been a diet trial only, the difference in MI incidence in the two groups would probably not have reached statistical significance. However, the chosen design for the study, which examined a combination of two important lifestyle factors, demonstrates clearly the effects of intervention and is also more relevant to usual medical practice.

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TOWARDS AN IMPROVED LIPID-LOWERING DIET: ADDITIVE EFFECTS OF CHANGES IN NUTRIENT INTAKE

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Summary To identify diets that are more effective than existing ones in reducing lipoprotein-mediated risk of atherosclerotic heart disease, the serum lipid and lipoprotein response to three modified diets was studied in twelve normal men living in an institution. The "Western" reference diet (40% energy from fat, P/S ratio 0:27) was compared in Latin square design with a fat-modified diet (diet B, 27% energy from fat, P/S 1:0, reduced cholesterol content), with a fat-modified diet supplemented with fruit, vegetable, and cereal fibre (diet C), and with a diet providing 40% energy from fat, having P/S ratio 1:0 and supplemented by fibre (diet D). The effects of fat modification and fibre-supplementation (diets C and D) were strongly additive—a fall in serum cholesterol by 24–29%, in low-density-lipoprotein (LDL) cholesterol by 31–34%, and in serum triglyceride by 21–26%; and the reduction, by diet C, of the ratio of serum cholesterol to high-density-lipoprotein (HDL)-cholesterol by 21%, and that of LDL-cholesterol to HDL-cholesterol by 26%. The additive effects of multiple changes in nutrient intake, each moderate in extent, permits the design of diets which are remarkably effective in reducing serum-cholesterol level.

Introduction

There is now much evidence that a raised serum cholesterol concentration is a causal factor in atherosclerotic heart disease (AHD) and a large body of data supports the view that it is desirable to reduce cholesterol levels in AHD-prone populations as a means of reducing risk from this disease. All proposals involve changes in diet. Increased physical activity is usually recommended, and for patients with major primary hyperlipidaemias drug treatment is often indicated. Each method of controlling hyperlipidaemia must be assessed for its efficacy, safety, cost, and acceptability for long-term use. Conventional dietary management of hypercholesterolaemia alone (without measures for reducing obesity) comprises restriction of intake to 25–35% of dietary energy and reduction of cholesterol intake to 150–250 mg per day. Most recommendations also include partial substitution of saturated fat by polyunsaturated fatty acids; recent guidelines propose a ratio of polyunsaturated fatty acids to saturated fatty acids (P/S ratio) of 1, though ratios of 1:5–2:2 were typical of earlier lipid-lowering diets.

The effects of dietary change on serum lipids is influenced not only by the composition of the diet but also by individual responsiveness, the type and genetic basis of the lipoprotein abnormality, and compliance and palatability. The 8–16% reductions in serum cholesterol achieved in clinical practice and in large-scale trials are smaller than those achieved in metabolic wards.

Many nutrients other than dietary lipids influence serum cholesterol levels. Some forms of dietary fibres, predominantly those derived from fruit and vegetables, such
as pectins, reduce serum cholesterol by 4–12% when consumed in large quantity. In a careful trial, replacement of proteins of animal origin by a vegetable protein, soy protein, reduced serum cholesterol by 6%. Several minerals and vitamins have also been said to lead to minor changes in serum cholesterol.

This report concerns attempts to identify diets that are more effective than existing ones in reducing serum-cholesterol levels, and thus in potentially reducing lipoprotein-mediated risk of ischaemic heart disease. Hence, detailed measurements of lipoprotein classes have been made. We have tested the hypothesis that the effects of various changes in nutrient intake on cholesterol metabolism are at least partly additive, as is the case for changes in fatty acid and cholesterol intake and probably so for fat and fibre consumption. We have also compared diets of differing fat content and fatty acid composition.

Methods

The dietary studies were carried out at the Maria Toevlucht Abbey at Zuiderd in the Netherlands. Twelve monks, aged 24 to 60 years, mean 45-1, volunteered to participate. They lived in the monastery, and apart from eating the prepared diets and undergoing regular blood tests and fecal collections, they did not change their daily pattern of work and devotions. Their relative body weights ranged from 0.79 to 1.19, mean 0.98. That all were in good health was supported by baseline routine biochemical findings, including serum thyroid levels. No intercurrent illness occurred during the study. The twelve participants were selected from a larger number of volunteers on the basis of their having the highest plasma-cholesterol levels within our reference range (up to 6.5 mmol/l), normal triglyceride levels, and very low alcohol intake.

Blood samples were drawn, with minimal stress, after an overnight fast. Serum was separated and disodium ethylenediaminetetraacetic acid (EDTA) was added (1 mg/1), samples were promptly cooled to 0–4°C and sent to St Thomas's Hospital, London, where analyses began within 10 h of venesection. Very low density lipoprotein (VLDL) was isolated by preparative ultracentrifugation at d = 1.006 g/ml. High density lipoprotein (HDL) was isolated by heparin-manganese precipitation; a portion of the supernatant was ultracentrifuged at d = 1.215 g/ml to yield the HDL2 subclass.

Cholesterol and triglyceride concentrations in serum and lipoprotein fractions were manually measured by standard enzymatic methods (Boehringer-Mannheim catalogue nos. 187313 and 166448, respectively) with duplicate analyses at the end of each period. Usual quality control procedures were followed, and the coefficients of variation for cholesterol and triglyceride measurement were 1.8% and 2.7%. Apolipoproteins B, A1, and AII were assayed by rocket immunoelectrophoresis.

A computer data bank of Dutch food composition was used to design four diets providing the nutrient intakes shown in the accompanying table. Normally available foods were selected, single batches being purchased when practicable. Duplicate portions of the diets were directly analysed at the University of Wageningen to check their conformity with the planned nutrient intakes. The types of food were restricted to those allowed by Trappist rules. The major foods making up the reference diet A were cheese, whole milk, white bread, butter, diet margarine (linoleic acid 60% of fatty acid content), eggs, rice, fruit, vegetables, semolina, cream, Dutch honey cake, golden syrup, sucrose, and an "instant" pudding. The fat-modified diet B differed from diet A in the proportions of these constituents, and in substitution of skimmed milk for whole milk and of a diet margarine for most of the butter. The fibre-enriched fat-modified diet C had greater amounts of apples, oranges, and bananas than diet B, and partial substitution of whole-wheat bread for white bread; brown beans were included and intake of other vegetables was greater. The high-fat, fat-modified, fibre-enriched diet D included less bread and potato, but more whole milk and diet margarine, than did diet C.

Two dieticians prepared the individual diets each day in a separate area in the monastery kitchen. The diets were planned so as to be precisely isocaloric with the estimated energy intake of the participants as assessed by 24 h dietary recall. The subjects' energy intake ranged from 1550 to 4250 (mean 2937) kilocalories/day and was given as three meals per day plus snacks in a few cases. One change was made in the course of the study on grounds of inappropriate hunger or satiety or because of weight trends. In addition, four batches of gruel were prepared daily, of composition conforming to the diets in the table; participants were instructed to eat portions of this, if necessary, to provide satiety. The dietary schedule made it possible for all subjects to maintain body weight within ± 1 kg except in the first 2 weeks, when most subjects lost 1–2 kg.

Diet A, the reference diet, was designed as a typical "Western" diet, providing 40% energy as fat with a P/S ratio of 0.7, and 617 mg of cholesterol in a 2500 kcal diet. Diet B was representative of a conventional but fairly strict fat-modified or "provident" diet for reduction of plasma cholesterol (27% energy from fat, P/S 1.0, cholesterol 245 mg, pectin 1.8 g). Diet C was closely similar to diet B except in two respects: it provided 3–4 times more dietary fibre, with emphasis on fruit and vegetable fibre, and half instead of a third of the protein was of vegetable origin. Diet D differed from diet C only in that there was no restriction of total fat; the P/S ratio (1.0), cholesterol content (245 mg at 2500 kcal), and fibre, pectin, and vegetable protein content of diets C and D were similar, but the fat content of diet D (40% of energy) resembled that of the Western diet A.

Each feeding period lasted 5 weeks. Every participant consumed all four experimental diets; the subjects were divided into four groups of three, each group receiving one of the four diets in turn in Latin square design, in the sequence ABCD, BCDA, CDAB, or DABC. The data of the Latin square were analysed by regression techniques to perform the analysis of variance, with the computer package GLIM. Since there was a reasonably steady state from the end of week 3, we treated values from weeks 2 to 5 as within-subject replicates in most cases.

Results

Lipid and lipoprotein levels at the end of each feeding period are illustrated in the accompanying figure. Compared with those during diet A, serum-cholesterol levels were lower during the three modified diets (p<0.01); the reductions during consumption of the fat-modified fibre-rich diets C (−29–2%) and D (−24–6%) were greater than that during the conventional fat-modified diet B (−21–6%; p<0.01, p<0.05, respectively). Similarly, serum-triglyceride concentration was significantly lower on diets C and D than on diet A or B (p<0.05 and p<0.01, respectively). Serum cholesterol was lowest during consumption of the fibre-rich fat-modified diet C, in which fat comprised 27% of food energy and carbohydrate 59%, while diet D (40% energy from fat, 47% from carbohydrate) was associated with the lowest serum-triglyceride levels (−26–4%).

LDL-cholesterol changes paralleled those of total serum cholesterol, decreasing by 26–5% on diet B, 34–5% on diet C, and 31–5% on diet D (p<0.01 for each, compared with the

NUTRIENT COMPOSITION OF THE REFERENCE DIET AND THREE EXPERIMENTAL DIETS

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (% of energy)</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Vegetable protein (% of protein)</td>
<td>34</td>
<td>34</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Fat (% of energy)</td>
<td>40</td>
<td>27</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Linoleic acid (% of energy)</td>
<td>4–6</td>
<td>8–1</td>
<td>8–1</td>
<td>8–1</td>
</tr>
<tr>
<td>Polyunsaturates (% of energy)</td>
<td>5–2</td>
<td>8–5</td>
<td>8–5</td>
<td>8–5</td>
</tr>
<tr>
<td>PS ratio</td>
<td>0–27</td>
<td>1–00</td>
<td>1–00</td>
<td>1–00</td>
</tr>
<tr>
<td>Cholesterol (mg/2500 kcal)*</td>
<td>167</td>
<td>245</td>
<td>252</td>
<td>245</td>
</tr>
<tr>
<td>Available carbohydrates (% of energy)</td>
<td>46</td>
<td>59</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Dietary fibre (g/2500 kcal)*</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Pectin (g/2500 kcal) as polysaccharides</td>
<td>1–2</td>
<td>1–8</td>
<td>6–3</td>
<td>6–3</td>
</tr>
</tbody>
</table>

Alcohol intake was negligible.

*Energy intakes varied from 1550 to 4250 kcal/24 h. **Monosaccharides and disaccharides contributed 16–20% energy in all four diets.
Serum lipid and lipoprotein concentrations (mean ± SEM in relation to type of diet).

Nos. given at top of columns refer to changes in levels. Cholesterol/HDL cholesterol ratio was 4.49 for diet A, 4.02 for diet B, 3.56 for diet C, and 3.56 for diet D. LDL cholesterol/HDL cholesterol ratio was 17.7 for diet A, 19.9 for diet B, 15.1 for diet C, and 15.8 for diet D.

reference diet). The reduction was greatest with diet C; LDL-cholesterol levels were lower during diets C and D than during diet B (p<0.01 and p<0.05, respectively). Serum-triglyceride levels reflected changes in VLDL-triglyceride which decreased by 19% on diet C and by 38% on diet D. HDL-cholesterol, and to a smaller extent HDL2-cholesterol, were lowered by diets B, C, and D, compared with diet A. The decrease in HDL-cholesterol with diet D (−5.5%) was small but those on diets B and C were significant (p<0.01). Diet C resulted in the smallest decrease in the HDL2 subclass (11.5%, NS) while diets B and D reduced HDL2-cholesterol concentration significantly (p<0.01 and p<0.05, respectively). On diet C the ratio of total serum-cholesterol to HDL-cholesterol fell by 21%, and that of LDL-cholesterol to HDL2-cholesterol fell by 26%.

No untoward effects were reported during consumption of the four diets.

Discussion

A major purpose of this study was to define diets that are more effective than existing ones in reducing serum cholesterol concentration, and hence likely to have a better potential for decreasing AHD risk. Because the various classes of plasma lipoproteins differ in their physiology and pathological associations, it is necessary to consider the effects of these diets on individual lipoproteins. LDL, which transports 60–70% of circulating cholesterol, is strongly implicated in the pathogenesis of AHD on epidemiological24 and experimental25 grounds. The role of VLDL, the main vehicle for plasma triglyceride of endogenous origin, is more controversial: although clearly a risk factor for AHD, its predictive power may not be independent of that of other lipoproteins.26 HDL-cholesterol levels are inversely and independently predictive of AHD risk,26,27 and a recent study indicates that levels of the small HDL2 subclass of HDL, but not of HDL2, discriminate between groups of patients with and without severe coronary atherosclerosis.28 VLDL and HDL metabolism are closely linked,7,29 and are partly controlled by common determinants.30

The three experimental diets were compared with diet A, a reference diet similar to habitual food patterns in the U.K., U.S.A., and most of Western Europe. Diet B was typical of a conventional, fairly strict “fat-modified”, lipid-lowering diet. Under the controlled conditions of this study, diet B resulted in lower serum and LDL-cholesterol levels than did diet A; HDL-cholesterol, especially the HDL2 subclass, was also reduced. Diets C and D were designed to answer the following questions: (1) Since plasma-cholesterol levels are reduced by a diet low in saturated fat and with an increased P/S ratio, and also by diets supplemented with gel-forming fibre such as pectins,12,14 were the effects of these dietary modifications additive? (2) If so, was the effectiveness further influenced by the level of fat intake, i.e., 27% of dietary energy typical of many Mediterranean diets3 vs 40%, the level typical in Western Europe and North America? Diet C (27% fat, fibre-enriched) was the most effective in reducing cholesterol levels in serum and in LDL, the latter remarkably by 34–55%; VLDL and serum triglyceride levels also fell, HDL-cholesterol decreased as with diet B, but HDL2 cholesterol did not change significantly. Diet D (40% fat, fibre-enriched) was of intermediate effectiveness in reducing serum cholesterol and LDL-cholesterol and of greatest potency in decreasing VLDL-triglyceride (by 38%); it did not reduce HDL-cholesterol significantly, though it reduced the HDL2 subclass more than did diet C. Although the experimental design does not permit quantitative assessment of the interaction between the modified fat and cholesterol intake and the supplementation with fibre (i.e., whether these modifications were fully or partly additive or synergistic), it is clear that diets C and D, particularly the former, are very effective in reducing LDL-cholesterol, in decreasing the LDL/HDL and LDL/HDL2 ratios, and in reducing serum triglyceride. From the epidemiological associations and physiological functions of these lipoproteins,5,7,26–28 diets such as C and D might be expected to reduce the lipoprotein-mediated component of AHD risk substantially.

Probably more than one characteristic of diet C contributed to the greater fall in serum-cholesterol produced by this diet than by diet B. Diet C was enriched with dietary fibre. When consumed as fruit and vegetables or as pectin or hemicellulose,12,15,31 fibres, mainly those classified as noncellulosic polysaccharides, reduce serum cholesterol by 0.17–0.8 mmol/l in normal subjects. In one study on hypercholesterolemic patients, 40–50 g pectin reduced cholesterol levels by 1 mmol/l.13 Diets C and D also had higher ratios of vegetable protein to total protein compared with diets A and B. Complete substitution of soybean protein for other dietary proteins has been reported to reduce serum-cholesterol by 6–24% in different studies, varying with the baseline serum-lipid levels and the degree of dietary control.15,16,32

In the present investigation, soy protein was not used, and only partial substitution of vegetable proteins for animal proteins was introduced. The vegetable protein contents of diets C and D were 52% and 45%, compared with about 34% in diets A and B.

In practice, dietary recommendations do not reduce mean serum-cholesterol concentrations in free-living people to levels associated with minimum AHD risk within Western populations (5–5.5 mmol/l),33 and still less to those of communities in which AHD is uncommon (4–5 mmol/l).34 Regression of experimental atherosclerosis in primates occurs at cholesterol levels of about 5 mmol/l.35 Hence nutritional patterns of improved effectiveness, such as the multifactorial dietary changes in this study, seem desirable.

The choice of institutional residents for the study was justified because it meant that all meals could be prepared and served in the subjects' normal environment, and that participants could continue with their habitual level of physical activity, and were likely to show very good
CONTROLLED Trial of Argon Laser Photocoagulation in Bleeding Peptic Ulcers

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Summary
The efficacy of argon laser photocoagulation in the endoscopic control of haemorrhage from peptic ulcers was tested in a controlled trial at two centres in London. Of 330 patients consecutively admitted with acute upper gastrointestinal tract haemorrhage, 76 were seen at endoscopy to have a peptic ulcer accessible to laser therapy and stigmata of recent haemorrhage. These patients were included in the trial. Identification of the exact source of haemorrhage within the ulcer crater was achieved by use of standard endoscopes with careful washing. Patients were stratified into three groups: ulcers with a visible vessel (52 total, 11 actively spurting); those without a vessel (17); and those with an overlying clot persisting after washing (7). Of the 52 patients with a visible vessel, 8 of 24 treated with the laser and 17 of 28 control patients had a further haemorrhage. 7 control patients died after an episode of reblooding, but no treated patients. Treated and control patients were well

REFERENCES

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