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Reviews and news on the role of lipids in Coronary Heart Disease

LIPID REVIEW

Nutritional Determinants of Coronary Heart Disease Risk

The incidence of coronary heart disease (CHD) varies widely between populations [1]. When people move from a country of low to one of high incidence, their susceptibility to the disease rapidly approaches that of the population already present [1], suggesting that environmental rather than genetic factors cause the high frequency of premature heart disease in affluent countries. Diet is one of the best established of these environmental factors.
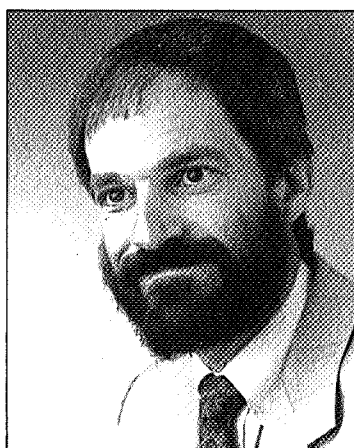
In addition to its effects on blood lipids and body fatness, diet may promote or inhibit coronary atherosclerosis through its effects on blood pressure and blood coagulation. However, the link via blood lipoprotein concentrations is the one for which the evidence is strongest; it is corroborated by the consistent results of epidemiological studies, controlled intervention trials, and clinical and biochemical investigations.

However, there is evidence of other health benefits from dietary modifications. For example, fat-modified diets may lower blood pressure in hypertensive patients. Similarly, an increased intake of unprocessed food plants may be of benefit in the treatment of type II diabetes and of obesity. Such a diet will also relieve constipation, a minor but widespread complaint.

Does CHD result in part from diet?

A major part of the variation in CHD mortality rates between countries is explained by differences in diet and is not related to differences in the provision of medical care. In fact, countries such as Sweden, where high-technology medical care is readily accessible, have much higher CHD mortality rates than the countrysides of Greece and Japan of 30 years age.

Within populations, as opposed to between populations, plasma lipoprotein concentrations strongly predict an individual's chance of developing
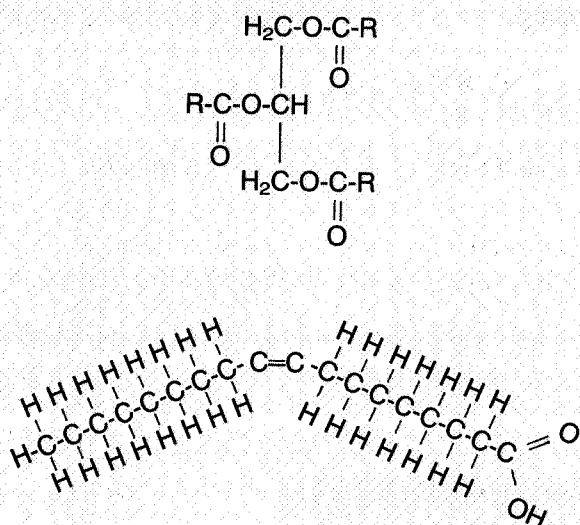
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heart disease [2], but relations between diet and CHD, and between diet and plasma cholesterol, are weak or difficult to demonstrate [3]. In part, this is a question of methodology: within western populations, long-term average nutrient intakes differ little between individuals while day-to-day fluctuations in intake are large. This makes it difficult to rank people according to their intakes of saturated fat and cholesterol [3]. Still, significant correlations between diet and cholesterol within populations, of the order of $r=0.10$ to 0.20, are found regularly [5,6]. The degrading effect of the ranking problem can be quantitated and corrected for [3], yielding true correlations of 0.20 to 0.30. This implies that a significant but small part of the variation in cholesterol within populations is caused by differences in food intake. A major part of the remaining variation must be due to differences in susceptibility to the effect of the omnipresent high saturated fat diet; hence the term 'polygenic hypercholesterolaemia' [6] to describe the widespread mild

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In next month's issue

"Guidelines for the Management of Hyperlipidaemia"

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Fig. 1 Structural formula of a triglyceride (fat) molecule, and of oleic acid as an example of a fatty acid. The natural *cis*-isomer of oleic acid has a bend at the site of the double bond.

Fig. 2 Structure of various fatty acids (Figs 1 and 2 reproduced after Gottenbos JJ, *Voeding* 1981; 42: 77, by permission)
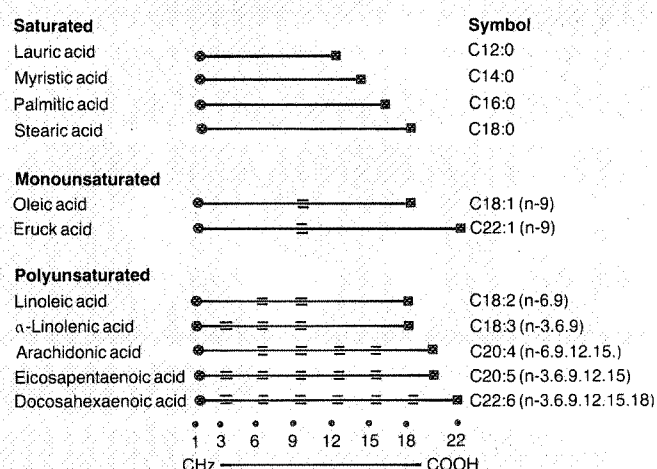
hypercholesterolaemia seen in affluent western countries. When there is little true variation in long-term nutrient intake, the other factors, both environmental and genetic, will determine an individual's position in the serum cholesterol distribution. This is analogous to body stature: malnutrition is an important cause of stunting, but once all children receive an adequate diet, differences in height become mostly a matter of heredity.

The question of interest, however, is whether switching to the diet eaten by populations or groups with a low CHD incidence will reduce the risk of premature coronary disease. There are many indications that it will.

Fats and fatty acids in the diet

Dietary fats consist largely of triglyceride molecules, each comprised of three long fatty acids esterified with glycerol (Fig. 1). The number, location and geometry of double bonds in these fatty acids (Fig. 2) have a profound effect on plasma lipid levels in man. The mechanisms responsible for this are not yet well understood [7] but the effects are quite reproducible [8,9] and they can be summarized in empirical formulae, such as Keys' formula (Panel).

Unsaturated fatty acids are fatty acids with one (mono) or several (poly) double bonds. Double bonds cause bends in the carbon chain (Fig. 1) which interfere with crystal formation and keep the fat liquid, i.e. an oil. Such double bonds will react with oxygen from the air, making the fat rancid, or with hydrogen, making it saturated. Saturation of oils with hydrogen is performed chemically in margarine factories, but also by bacteria in the rumen of cows and sheep. Saturated fatty acids have only single bonds and straight chains that crystallize easily. Hence butter and brick-type margarines made from hydrogenated oils are hard,

Keys' formula

Keys formula summarizes the results of a large number of controlled studies on the effect of changes in dietary lipids on serum cholesterol [9,15,25]. When converted to SI units, it reads:

$$\Delta \text{ Serum Cholesterol (mmol/l)} =$$

$$0.035 (2\Delta S{-}\Delta P) + 0.08 \, \Delta \sqrt{\text{chol/MJ}}$$

Δ = change

S = % of energy provided by saturated fatty acids (especially lauric, myristic and palmitic acid)

P = % of energy from polyunsaturated fatty acids

chol/MJ = cholesterol intake in milligrams per megajoule

while chicken fat, which contains more double bonds, is soft. The body and milk fats of cattle and sheep are typically high in saturated fat, part produced from dietary polyunsaturates in the rumen but most representing storage of excess calories. The meat of wild animals such as kangaroos or buffaloes is low in fat, presumably because they eat less and move more than farm animals.

Most plants store their spare energy as starch, but certain high-fat seeds and fruits cultivated in vast amounts produce fats that may be predominantly saturated (coconut, palm, palm kernel), monounsaturated (olive, rape seed) or polyunsaturated (sunflower, soya, corn).

Effects of fats and fatty acids on lipoproteins

In feeding experiments, fat cannot simply be added to the diet; something has to be left out to keep energy intake constant and, as shown in Table 1, the omission

Addition	Composition of the diet				Predicted-cholesterol
	Fat			Cholesterol	
	Total	Sat.*	Poly.*		
	(% of energy)			(mg/MJ)	(mmol/l)
None (basal diet)	38	15	6.5	24	—
25 g of olive oil, replacing butter	38	11	7.0	17	−0.4
25 g of olive oil, replacing potatoes and bread	47	16	7.1	24	0.0
Two eggs, replacing cheese and meat	37	13	6.7	71	+0.1
Two eggs, replacing toast and jam	42	16	6.8	76	+0.4

* sat. = saturated fatty acids;   poly. = polyunsaturated fatty acids.

Table 1. The effect on cholesterol of added foodstuffs, if different foods are replaced. The predicted change in serum cholesterol was calculated from Keys' formula. The basal diet provided 10 MJ (2400 kcal) per day.

determines the resulting serum cholesterol change as much as the addition. Several trials [10-12] have shown that the most effective dietary measure to lower total and LDL-cholesterol is to remove foods high in saturated fat and replace them with unsaturates. Two-thirds of the resulting drop in cholesterol is attributable to the saturated fatty acids removed, and one-third to the polyunsaturates added (Panel). The fall in cholesterol is largely caused by an absolute reduction in the concentration of LDL, but percentage-wise the fall in VLDL, and thus in fasting triglyceride, is larger [13]. Provided that polyunsaturates contribute no more than 10% of energy, there is no change or only a small reduction in HDL [14].
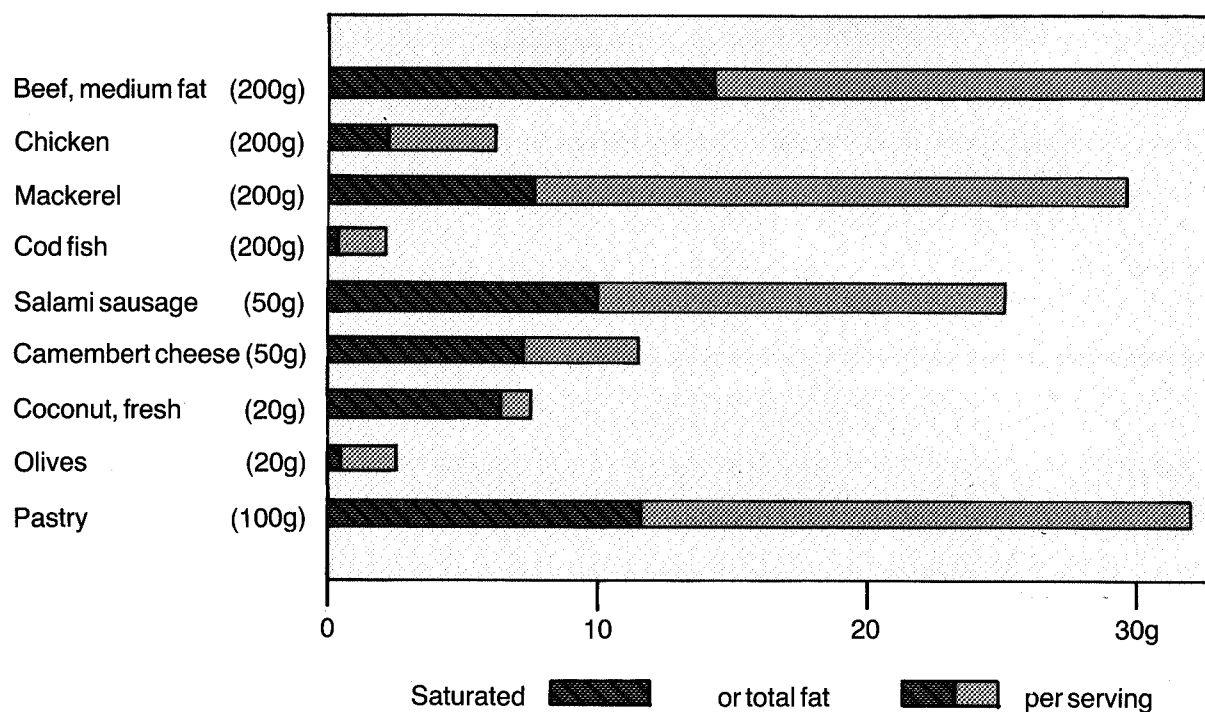
The effects of saturated fatty acids are limited to those with a length of 12, 14 or 16 C-atoms; C8 and C10 (medium-chain triglycerides) and C18 (stearic acid, abundant in cocoa butter) fatty acids do not raise cholesterol [15,16].

Olive oil is rich in the monounsaturated fatty acid oleic acid, as are new types of rapeseed and other seed oils. When added to the diet, these tend to displace saturated fats and thus lower cholesterol (Table 1). Recent findings based on the use of liquid formula diets suggest that oleic acid-rich oils may lower LDL as effectively as polyunsaturated oils, without lowering HDL [17]. However, experience with polyunsaturates covers 30

years of controlled trials, several of which are of sufficient duration and size to establish clinical benefits [18,19]. For monounsaturated oils, such data are not yet available. Epidemiological data on olive oil and heart disease [20] suggest a highly beneficial effect but cannot prove a causal relationship.

The (n-3), or omega-3, polyunsaturates found in fish form a separate class of essential fatty acids, distinct from the (n-6) fatty acids. Cold sea fishes accumulate (n-3) polyunsaturates, such as eicosapentaenoic acid (EPA; Fig. 2), from the plankton they eat, possibly to serve as an 'anti-freeze'. Fish oils rich in (n-3) fatty acids lower serum triglyceride and VLDL very effectively. Data on their effect on LDL are scarce and contradictory; in hypertriglyceridaemic patients, they may even elevate LDL when compared with oils rich in (n-6) fatty acids [21]. Fish oil consumption decreases blood coagulation and may thus help to prevent thrombosis and atherosclerosis. However, proof of the long-term safety and efficacy of fish oil preparations in man is still lacking [22].

The amount of (n-3) polyunsaturates provided by a normal varied diet rich in sea food is only about 1 g per day. Whether such an amount will reduce CHD risk is uncertain although epidemiological data are encouraging [23]. However, even fatty fish tends to be lower in saturated fat than pork, beef or lamb (Fig. 3).

Fig. 3 Saturated and total fat content of typical servings of selected foodstuffs. Note that animal fats are not necessarily high, and plant fats are not necessarily low, in saturates.

Fish is also a good source of iodine, vitamin D and absorbable iron - nutrients that tend to be in short supply in many people's diet.

Large amounts of fish oil go into the preparation of cheap margarines, but these are hydrogenated and contain little, if any, (n-3) fatty acids.

Cholesterol in the diet

Eggs

Dietary cholesterol is less hypercholesterolaemic in man than in rabbits or monkeys, but most experts agree that the effect in man is not negligible [24]. Keys' formula predicts that if an amount of cholesterol equivalent to two eggs a day is added to a moderate-cholesterol diet, the serum cholesterol level will rise by around 0.28 mmol/l or 5% [25] - the extent of the change depending on what the eggs replace in the diet (Table 1). Most of the rise is caused by an increase in LDL, but HDL levels may also rise [26,27]. In animals, cholesterol feeding induces formation of the highly atherogenic β-VLDL or IDL, and similar findings have been described in man. Epidemiological data on dietary cholesterol are scanty [28] but do uphold the relation with serum cholesterol. There is a biological variation in the susceptibility of serum cholesterol to dietary cholesterol, but most people show some rise if investigated long and thoroughly enough [27]. Apparent hypo- or hyper-responsiveness occasionally disappears if subjects are retested [29]. Patients with familial hypercholesterolaemia are at least as susceptible to dietary saturated fat and cholesterol as healthy subjects [30]. However, diet is insufficient to normalize serum levels in this disease which is genetic and does not result from a faulty diet.

The hypercholesterolaemic effect of dietary cholesterol appears to be strengthened by saturated, and diminished by polyunsaturated, fatty acids in the diet [3. Switching to low-fat dairy products is, thus, an especially effective way to lower cholesterol since the fat in milk, cheese, yoghurt and cream is high in both saturated fat and cholesterol - it contains four to five times the amount of cholesterol found in other animal fats.

Eggs and liver are also high in cholesterol but, on the other hand they provide a wealth of vitamins and minerals [32]. A good compromise is to take two eggs per week and liver a few times per month.

Shellfish may be less hypercholesterolaemic than previously thought, especially molluscs such as oysters, clams and scallops which are lower in cholesterol than hitherto believed [33].

Sugar, starch and fibre

In controlled experiments, sugar and starch will lower total cholesterol if substituted for saturated fat in the diet. In actual life, sweet foods high in refined sugar, such as cakes and pastry, tend also to be high in saturated fat, cholesterol and calories. On the other hand, unprocessed starchy foods, like beans, bread and potatoes, and foods rich in natural sugars, such as fruits and vegetables, contain little fat, most of which is unsaturated. Fruits, vegetables, legumes and oats also contain other factors that lower cholesterol [34,35]; of these, gel forming fibre components such as pectin are most reliably identified. Wheat bran does not favourably affect blood lipids.

The foregoing may explain why, in international comparisons, serum cholesterol levels and CHD rates

are correlated negatively with intakes of starchy foods but positively with sugar consumption [36].

High-carbohydrate diets lower both LDL and HDL levels, while VLDL and serum triglycerides may rise [14]. The low heart disease rates in populations with a high intake of complex carbohydrates [20] suggest that these hypothetically adverse effects on HDL and VLDL are overridden if LDL is low enough or that they are cancelled out by other life-style factors, such as physical activity.

Miscellaneous foods
A moderate intake of *alcohol* increases HDL. There is weak epidemiological evidence for a beneficial effect on CHD rates. Higher intakes of alcohol promote hypertriglyceridaemia and, perhaps, hypertension [36]. In addition, alcohol abuse is a prime cause of accidents, violence, liver cirrhosis and pancreatitis, and there is good evidence for a relation with oral and oesophageal cancer.

There is, therefore, no need to force abstinence on CHD patients, but encouraging alcohol use to prevent CHD would be an unsound public health policy.

There are some indications that *coffee* may raise serum cholesterol [37] and CHD risk [38], but the data are preliminary and contradictory

Garlic and *onion* are widely consumed by populations with a low rate of heart disease, but evidence for a direct beneficial effect is lacking. Neither *vitamin E* nor other vitamin preparations are effective in the control of hypercholesterolaemia [39]. In well-controlled trials, the effects of *lecithin* preparations are not appreciably larger than those of their constituent fatty acids [40] which can be bought as oils at a fraction of the price of lecithin.

Obesity
Obesity is associated with a depression of HDL and with elevations of VLDL, LDL, glucose, uric acid and blood pressure. In addition, obesity is a risk factor for CHD even in people with normal blood lipids and blood pressure. The male or central type of obesity, with fat deposited on and inside the abdomen, is associated with a higher risk than the peripheral fat accumulation typical of women [41]. The dramatic rise of LDL-cholesterol with age in affluent populations - typically some 50% between ages 20 and 50 [42] - may also be partly due to increases in body mass.

Formal proof that weight loss by itself improves the lipoprotein profile has been hard to obtain because permanent weight reduction is so difficult to achieve. Prevention is probably the only way to combat this risk

factor which, unlike smoking, hypercholesterolaemia and hypertension, shows no sign of declining in population groups at high risk for CHD.

Practicality and adequacy of the preventive diet
A diet low in saturated fat and cholesterol can be realized in many ways. Traditional Chinese and Japanese cuisine is very low in fat, but some modifications are required to reduce the high salt and sodium glutamate content of dishes. The classic Greek and Italian food pattern is somewhat higher in fat but still low in saturates. The food served in pizza restaurants in North-Western Europe and the USA has the appearance of a traditional Italian dish but the high saturated fat content typical of affluent diets.

The various vegetarian styles of cooking offer a third type of diet low in saturated fat. The nutritional value of vegetarian diets can be improved by occasional consumption of moderate portions of fish and lean meat at the expense of cheese and eggs.

The diet patterns of the Far East, the Mediterranean and of vegetarian groups in western countries have been practised for many years and are associated with markedly reduced rates of CHD and, in Japan, Greece [20] and western-style vegetarians [43], with prolonged longevity. Diets reduced in saturated fat and cholesterol and enriched in unprocessed plant foods can lower total cholesterol by 20–30% in some patients [34], and LDL by more than that [44].

Replacement of the calories from saturated fats by lean animal products and food plants will, in principle, increase the intake of essential nutrients. Intakes of (n-3) and (n-6) essential fatty acids, carotene, folic acid, iodine and vitamins C, D and E will increase. Vitamin B1 is contributed in sufficient amounts by whole wheat bread, pulses and nuts, and vitamin B2 and calcium are provided by low-fat dairy products (note that the main nutrients from cow's milk are found in the water-phase, not the fat).

Protein is seldom a problem because almost any reasonably varied diet provides enough of all the essential amino acids. Those who for moral reasons do not wish to eat meat and fish should, however, watch their iron and zinc intake. Absorption of iron from plant foods is poor, although it can be improved by the simultaneous intake of vitamin C for example, as fruit juice. Vegans, who refuse dairy and egg products as well as animal flesh, should take vitamin B12 supplements.

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Annotation

Cholesterol synthesis and LDL clearance

Dietschy and his colleagues have performed an important series of investigations to clarify the contributions made by sterol synthesis *in situ* and low density lipoprotein (LDL) uptake to the needs of various tissues for cholesterol. They studied several animal species with markedly different rates of hepatic sterol synthesis. Cholesterol synthesis was measured by incorporation of tritium-labelled water into digitonin-precipitable sterols (DPS). This activity can be measured in various tissues both *in vivo* and *in vitro*, and the technique avoids errors associated with the alternative use of labelled acetate, namely differential dilution of the specific activity of ^{14}C acetyl-CoA. A constant perfusion procedure was used to study lipoprotein uptake by the liver and other tissues.