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

REVIEW

# Dietary Fatty Acids and Cardiovascular Risk

The term 'dietary fat' includes a large number of different lipids. Some are present in minuscule amounts, such as vitamin D, of which an intake of 0.00001 grams per day is ample. Others, such as phospholipids, are consumed in gram amounts. However, the bulk of edible fats and oils is made up of triglycerides. Each triglyceride consists of a glycerol molecule to which are attached three fatty acid molecules. This esterification with glycerol neutralizes the acid moieties of the fatty acids, which would otherwise damage cell membranes. Most people will consume some 40 to 200 grams of esterified fatty acids per day, the amount depending on caloric requirements and food preferences.

Fats are often considered to be just fuels. Fats do provide an important share of dietary energy, but they also bear a similarity to dietary proteins in that they include essential nutrients. Some fatty acids are essential, just as some amino acids are essential, because they are needed as structural components or as signal molecules in the body. Others serve only as fuel. The various fatty acids, essential and non-essential, have a variety of physiological effects, many of which relate to the cardiovascular system. The accompanying Panel (overleaf) explains some terms describing fatty acids, and Table 1 enumerates the major fatty acids, their structure, and their occurrence in food.

Blood and tissue fatty acids and coronary risk

The human body rearranges nutrients in such a way as to preserve its identity and the characteristic composition of its tissues. However, some food molecules do make their way into our tissues unchanged, notably fatty acids:

— Among Cretan children, who have a large dietary intake of olive oil, the proportion of the
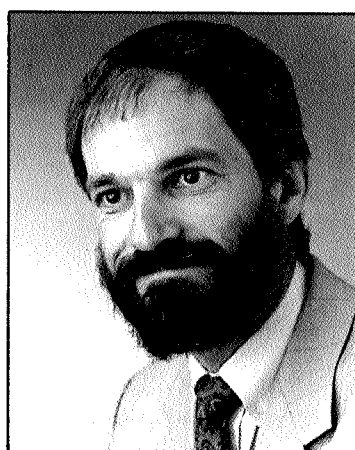
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monounsaturated fatty acid oleic acid (see Table 1) in blood cholesterol esters is almost 50% higher than in Dutch children, who have a much lower intake of this type of fatty acid [1];

— Eating fatty fish causes a marked increase in the proportion of eicosapentaenoic acid (EPA) in platelet and erythrocyte membranes;

— The proportion of linoleic acid in subcutaneous storage fat corresponds to that in the dietary fat throughout the range 8% to 55% [2].

Tissue fatty acids thus form a basis for studying relations between dietary fatty acid and coronary heart disease (CHD).

Lewis was the first to report that patients with ischaemic heart disease had a low proportion of

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In next month's issue

Diabetes mellitus, Hyperlipidaemia and Atherosclerosis

EL Bierman, University of Washington, Seattle, USA.

Fatty Acid Terminology

Saturated/unsaturated. A fatty acid is made up of a chain of 6 to 26 carbon atoms, 18 being the most common length. Every carbon atom has four bonds, each of which must link with some other atom. A typical carbon atom will enter into one bond with its left-hand carbon neighbour and one with its right-hand carbon neighbour, and the two remaining bonds will each bind one hydrogen atom (Figure 1a). Such a molecule is described as 'saturated'. Carbon-carbon pairs can also join by a *double bond*, so that each carbon partner now has only one bond to bind hydrogen (Figure 1b).

Figure 1a:
Saturated bonds

Figure 1b:
An unsaturated bond
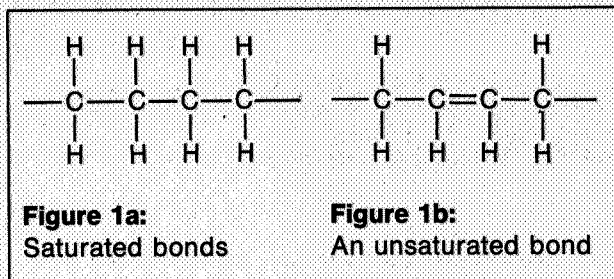
A fatty acid that contains such double bonds is 'unsaturated'. If it is reacted with hydrogen gas in the presence of a catalyst, one link of each double bond is broken, and the adjacent carbon atoms in each such broken bond now have one extra bond free to react with an extra hydrogen atom. When this process has been completed all carbon-carbon bonds are single and the fatty acid is saturated. This saturation or *hydrogenation* process takes place in the rumen of cows and sheep, where the unsaturated plant fatty acids from fodder are hydrogenated by bacteria. It is imitated in margarine manufacture where unsaturated vegetable and marine oils are hardened by hydrogenation to produce solid, relatively saturated fats.

N-6 and n-3 fatty acids. The human body has enzymes that can abstract two hydrogen atoms from neighbouring carbon atoms and thus convert saturated (Figure 1a) into unsaturated (Figure 1b) fatty acids. However, unlike plants, the human body is unable to produce double bonds located six or fewer carbon atoms from the terminal carbon atom (ie the one farthest from the acid group). Chemists designate this terminal carbon as 'n' or 'ω'. Thus we can make oleic acid from stearic acid, but not linoleic from oleic (see Table 1) because linoleic acid has its highest double bond at the n-6 ('n minus 6') position. Therefore, linoleic acid has to be provided by plant foods. Inside liver cells, linoleic acid is converted into a variety of fatty acids with double bonds in various places but none closer to the terminal carbon than n-6. Similarly, α-linolenic acid and the 'fish fatty acids' eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (acquired by fish from plankton) are part of a family of n-3 fatty acids that cannot be produced from linoleic or oleic acid.

Name of Fatty Acid	Formula[x]	Typical Intake[*] (g/day)	Example of Source
Medium-chain acids	C6:0 - C10:0	2	Coconut and butter fat
Lauric	C12:0	2	Coconut and palm kernel oils
Myristic	C14:0	8	
Palmitic	C16:0	30	Butter, cheese, palm oil, meat
Stearic	C18:0	15	Cocoa butter
Oleic	C18:1 (n-9)	32	Olive oil, pork fat, rapeseed oil
Elaidic	trans C18:1 (n-9)	6	Hydrogenated fats
Linoleic	C18:2 (n-6)	12	Sunflower oil
γ-linolenic	C18:3 (n-6)	0.1	Evening primrose oil
α-linolenic	C18:3 (n-3)	2	Soybean oil, vegetables
Eicosapentaenoic (EPA)	C20:5 (n-3)	0.3	Fish
Docosahexaenoic (DHA)	C22:6 (n-3)	0.1	Fish

Table 1. Characteristics of dietary fatty acids.

[x]The formula indicates the length of the chain and the number and location of double bonds. For example, C20:5 (n-3) has 20 carbon atoms and 5 double bonds; the first double bond starts at carbon atom 3, counting from the end of the molecule.

[*]As typically consumed by middle-aged men in the Netherlands.
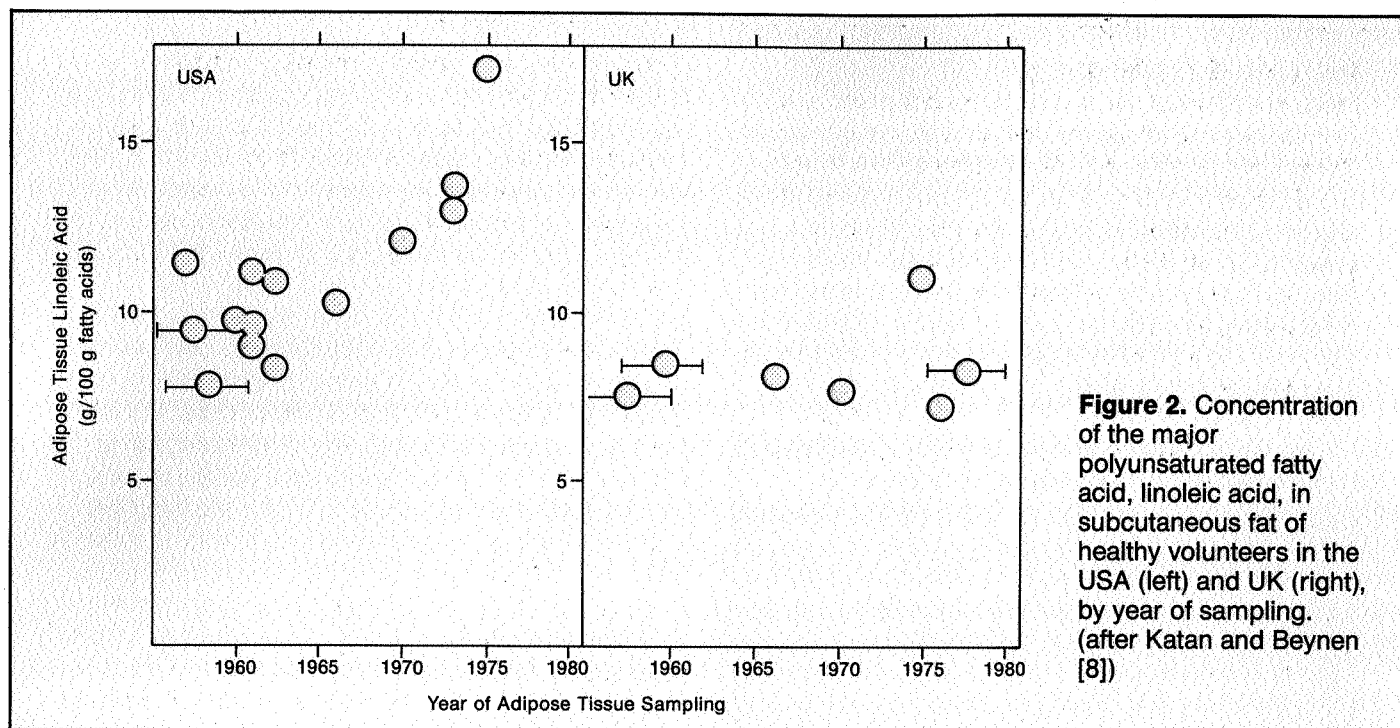
Figure 2. Concentration of the major polyunsaturated fatty acid, linoleic acid, in subcutaneous fat of healthy volunteers in the USA (left) and UK (right), by year of sampling. (after Katan and Beynen [8])

linoleic acid in their plasma cholesterol esters [3]. Subsequently, a longitudinal (ie predictive) study by Kingsbury and coworkers showed that a low linoleate content was indeed an independent predictor of myocardial infarction (MI) [4]. Similar findings were reported for other populations and for linoleate in other blood constituents and in adipose tissue [5-7]. In addition, Wood et al [7] found that the level of the n-3 fatty acid EPA was also lower in blood platelets of patients with angina than in those of matched controls (though not of patients surviving MI). At the population level, Katan and Beynen [8] noted that the decline in CHD in the USA had been preceded by a rise in the linoleic acid content of body fat in Americans. In the UK, neither the fat tissue composition nor the CHD incidence has demonstrably changed as yet (Figure 2).

Epidemiological associations are, however, fraught with pitfalls. Subjects or populations who eat a putatively 'healthy' diet might in fact be protected by other, coexisting habits and the high linoleic acid levels in tissues might simply be a confounding variable, correlating with a healthy life-style without contributing directly to protection against CHD. Indeed, Wood et al found that tissue linoleic acid levels were inversely associated with cigarette smoking, itself a major CHD risk factor [7, 9]. Therefore, epidemiological observations need to be supplemented by experiments.

Effects of fatty acids on plasma lipids and lipoproteins

Experimentally, the best established link between fatty acids and CHD involves their effects on plasma LDL-cholesterol concentrations and hence on risk of CHD. Fatty acids that are made up of 12, 14 or 16 carbon atoms and that lack double bonds (Table 1)

have a powerful elevating effect on plasma cholesterol [10]. These cholesterol-elevating saturated fatty acids are fairly rare in wild animals and plants but the foods that contain them have become much in demand and modern agriculture produces these foods in huge amounts. Cow's milk is a major source of C12-16 saturates. Fat-rich milk products, cheese and butter are major constituents of the diet in northwestern Europe and North America, and are becoming popular in the rest of the world, replacing traditional foods. Other major sources of saturated fatty acids include hard margarines (see Panel), meats from farmed land animals, and plant fats such as palm and coconut oil that are widely used in manufactured foods [11]. Replacement of these saturated fatty acids by other dietary fuels will consistently lower plasma LDL-cholesterol, and several large-scale controlled trials have shown that such dietary modification will also lower the incidence of CHD [12-15]. Nutrients that can take the place of saturated fatty acids are:

Carbohydrates. Carbohydrates, in the form of wheat, rice, other cereals and root vegetables are traditional staple foods. Populations consuming high-carbohydrate low-fat diets usually have low rates of heart disease. The health effects of high-carbohydrate (ie low-fat) diets in affluent populations have not, however, been formally tested in adequate controlled clinical trials. Also, there is now epidemiological and experimental evidence that such diets lower not only LDL- but also HDL-cholesterol, and that they elevate plasma VLDL and triglyceride [16-18]. On the other hand, these low-fat diets probably offer better protection against overconsumption of calories than diets higher in fats and oils [19]. The wisest course for the moment appears to be the replacement of saturated fatty acids partly by carbohydrates and partly by other fatty acids that do not elevate cholesterol.

Fatty acids. Many types of fatty acid may be considered as alternatives to saturates. The major ones are:

Stearic acid: Stearic acid is saturated, but, like the saturated medium-chain fatty acids (Table 1), it does not elevate plasma cholesterol [10,20]. However, foods that contain stearic acid usually also contain palmitic acid and other cholesterol-raising saturates; even the fat in chocolate (cocoa butter), which has an unusually high proportion of stearic acid, also contains just as much of the LDL-elevating C12-16 saturates as pork fat (lard). Thus, 'high in stearic acid' is no recommendation in itself. Geneticists and food technologists are becoming interested in replacing palmitic acid in artificially produced foods by stearic acid; however, the safety and lipid-lowering efficacy of foods high in stearic acid will need thorough scrutiny before they can be recommended as part of our daily diet.

Oleic acid: Olive oil, which is about 75% oleic acid by weight, has been a staple food in Mediterranean countries for millennia. This does not by itself prove that oleic acid promotes long life; mass longevity is a product of many aspects of 20th century life. Nonetheless, oleic acid does produce lower cholesterol levels than the cholesterol-elevating saturates such as palmitic, lauric, and myristic acid [21]. Also, the Seven Countries Study has produced epidemiological evidence for an inverse association between dietary oleic acid and ischaemic heart disease risk [22].

Linoleic acid: Linoleic acid is the major n-6 (or ω-6) polyunsaturated fatty acid. It is an essential fatty acid (ie the human body needs an exogenous source), but the amount needed is quite small and is provided by most diets. Several investigators have found that replacement of saturates by linoleic acid produces a more pronounced decrease in cholesterol than replacement by carbohydrates or oleic acid [10, 21], though more recent research has thrown some doubt on the putative advantage of linoleic over oleic acid [23]. Whatever the relative merits of linoleic acid, there is no doubt that replacement of saturates by linoleic acid effectively lowers LDL, and often also VLDL and triglyceride. Intakes up to the recommended maximum of 10% of total calories usually leave HDL concentrations unchanged [24].

γ-linolenic acid (GLA): GLA is a member of the (n-6) family; it is produced in the body from linoleic acid by insertion of a third double bond at the n-12 carbon atom (Table 1). Capsules of evening primrose oil, which is particularly rich in GLA, are available. The utility of these preparations in optimising plasma lipoproteins is unconfirmed [25].

N-3 (ω-3) fatty acids: The proportion of n-3 fatty acids in normal mixed diets is an order of magnitude lower than that of linoleic acid (Table 1). The large number of double bonds in n-3 polyunsaturates (three to six, as opposed to two for linoleic acid) makes them prone to oxidation and rancidity, and therefore the edible fats industry has shied away from producing them in bulk. Even fatty fish like salmon or mackerel do not provide more than 1-2 g/100 g. Purified fish oils, however, are now widely available in air-tight capsules, and they make it possible to consume the very-long-chain n-3 polyunsaturates, EPA and docosahexaenoic acid (DHA), in amounts corresponding to as much as several kilograms of fish per day. Fish oil effectively lowers VLDL and triglyceride, but recent reports from well-controlled trials show disconcerting elevations of LDL-cholesterol and apoB in patients treated with fish oil [26, 27]. If fish oil prevents coronary disease, it is despite its action on plasma LDL.

The other n-3 fatty acid is α-linolenic acid. It has not been tested extensively in man, but its action on plasma lipids appears to resemble that of linoleic acid. Rats effectively convert α-linolenic acid into EPA, but it is doubtful whether this happens in man.

Effects on blood pressure

Dietary essential fatty acids are obligatory precursors of prostaglandins and other eicosanoids, and prostaglandins influence blood pressure. Thus, it is plausible that dietary n-6 and n-3 essential fatty acids may influence blood pressure regulation.

Early studies [28] showed that linoleic acid lowered blood pressure in hypertensive rats. Human studies have, however, yielded contradictory results [29]. Most investigators failed to find an effect [30, 31], but some trials have shown a lowering of blood pressure by diets enriched in linoleic acid [32, 33]. The matter awaits resolution.

The very-long-chain n-3 polyunsaturates have been more difficult to study because of their instability. The availability of fish oil capsules has made experimentation easier, and several groups have now reported significant falls in blood pressure in patients treated with fish oil preparations [34, 35] (Figure 3). However, in a properly designed and controlled trial in healthy men, the effect on blood pressure of eating 135 g/day of mackerel was negligible [36].

Effects on coagulation and thrombosis

In rats, saturated fatty acids promote coagulation and thrombosis [37]. Stearic acid is particularly active in this respect; hence there are reservations concerning its suitability as a replacement for palmitic acid in foods. Linoleic acid is less thrombogenic than saturates in animals, and in humans, too, reduced
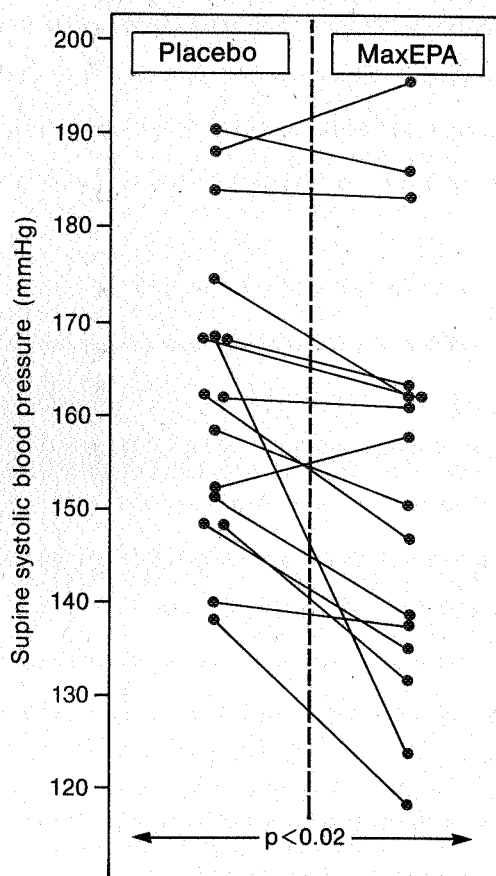
Figure 3. Individual changes in supine systolic blood pressure between sixth week of placebo (left) and sixth week of fish oil concentrate (16.5 g/day)(right) in 15 women and men with essential hypertension. (after Norris *et al* [35])

platelet aggregability and reactivity have been reported in response to high linoleate diets [38, 39]. The most powerful anti-thrombogenic effects are seen with the n-3 polyunsaturates EPA and DHA (reviewed in [40, 41]). Marked prolongation of bleeding time is produced not just by fish oil preparations but also by diets rich in fatty fish [42]. Whatever the cause of the bleeding tendency — reduced thromboxane formation or fish-oil-induced thrombocytopaenia [36] — fish diets could offer protection against MI in a manner analogous to aspirin. A study of the effect of fish oil on the rate of restenosis after percutaneous transluminal angioplasty has produced encouraging results [43]. However, the experimental evidence is still incomplete, and epidemiological findings are not consistent. For instance, the population of east Finland combines a high fish consumption with one of the highest rates of CHD in the world.

Thus the value of fish oil in the prevention of CHD is still unsettled. Fish oil is a potent substance with many actions, and for that very reason its widespread application must be preceded by rigorous testing in controlled clinical trials.

Effects on cardiac function

Studies have shown that linoleic acid favourably affects coronary blood flow and heart muscle function in rats [28]. More recently, it was also reported that linoleic acid may be anti-arrhythmic, and saturated fatty acids proarrhythmic [44–46]. Dietary n-3 fatty acids may be even more effective than linoleic acid in reducing the vulnerability of the myocardium to arrhythmic stimuli [46]. This is obviously a promising field.

Conclusion

Recent research on fatty acids has produced some remarkable findings, but it has not radically altered our thinking on the dietary prevention of CHD. Saturated fatty acids are still the villains of the piece, and unsaturated fatty acids the heroes, or at least the innocent bystanders. The potential of diet in the prevention and treatment of coronary disease has, however, been increased by current investigations. Different fatty acids can be used to treat different conditions; thus linoleic acid is more effective against hypercholesterolaemia, and EPA and DHA are more effective against hypertriglyceridaemia and possibly against thrombosis. Oleic acid may offer an extra choice both to individuals and to food manufacturers and chefs striving to prepare attractive lipid-lowering menus.

Other fatty acids, such as stearic and γ-linolenic acid are waiting in the wings. The food industry, spurred by developments in biotechnology and by public interest in healthy diets, is readying itself to produce foods with almost any fatty acid spectrum that science deems optimal. Nonetheless, we should proceed cautiously. The initial enthusiasm for fish oils was based largely on extrapolations from biochemical observations plus exaggerated claims about the health and longevity of Eskimos. Properly designed and controlled trials are only now taking place, and they have produced some welcome surprises but also several disappointments. In contrast, the beneficial effects of replacement of saturates by linoleic acid are supported by controlled trials with clinical end points, and by a giant 'natural experiment'; over the past 30 years, linoleic acid intake in the USA has doubled, with no evidence up to now of ill-effects [47], and at a time when CHD mortality has fallen steeply. Similarly, those favouring oleic acid can find support from data on the longevity of olive oil-consuming populations. Hard evidence in man should be required for other fatty acids before they are allowed to play a major role in our diet.

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