Dietary Fat and Chronic Diseases

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Dietary guidelines for the prevention of chronic diseases usually include several recommendations on fat intakes. This review, therefore, focuses on dietary fat intakes in relation to cardiovascular disease, cancer and obesity. Dietary guidelines on the type of fat to eat are issued in terms of the major classes of fatty acids, (saturated, monounsaturated and polyunsaturated fatty acids). However such advice may be over-simplistic considering the very variable effects of individual fatty acids - even those within the same class - on atherogenic and thrombogenic factors. This is particularly relevant in the case of trans unsaturated fatty acids which have more atherogenic effect on blood lipids than saturated fatty acids and therefore need to be considered separately to avoid confounding the assessment of the atherogenicity of fat intakes. The potentially undesirable effects of a low fat, high carbohydrate intake on blood triacylglyceride (raising effect) and HDL cholesterol (lowering effect) concentration, which may be offset by intakes of PUFA n-3 (oil fish), will also be explored. The variability of individual fatty acids, including trans, in terms of their impact on blood lipid concentrations, thrombogenic factors and cancer will be briefly discussed.

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Dietary fat intakes are implicated in the aetiology of many of the major diseases responsible for mortality in developed countries. Thus several components of dietary guidelines issued in these countries concern advice on the amount and type of fat that should be eaten (Table 1). In general populations are advised to reduce the total amount of fat consumed from an average intake of approximately 40% of total energy intakes to 30-35%[1,2]. Advice on the type of fat to eat is given in terms of the three major classes of fatty acids. Saturated fatty acids (SFA) should not exceed 10% of average energy intakes, polyunsaturated fatty acids (PUFA) should contribute up to - but not exceed - a further 10% of energy intakes, while monounsaturated fatty acids (MUFA) should represent the major type of fat eaten (10-15% of energy intake on average). In some countries, for example the UK and Ireland, more detailed advice is given where it is recommended that intakes of trans unsaturated fatty acids, which are estimated to contribute an average of 2% of energy in the UK, should not increase further, and that PUFA of the n-3 series should be increased.

Table 1. **Dietary guidelines on fat intakes**

Fat	*UK population*	*US NCEP1*	*US NCEP2*
Total fat (%)	</=33	<30	<30
SFA (%)	</=10	<10	< 7
MUFA (%)	--	10-15	10-15
PUFA (%)	< 10 (n6+n3)	<10	<10
Trans (%)	</=2		
Cholesterol (mg/day)	245	<300	<200

The rationale for these recommendations is mainly based on what is known about the relationship between diet and cardiovascular disease where an extensive field of research focuses on fat intakes in particular. Diets which provide a high proportion of energy intake as fat contribute to the development of obesity, especially in cases where physical activity levels are low. Obesity and low physical activity levels are, in turn, major risk factors for Non-Insulin-Dependent Diabetes Mellitus (NIDDM). Both obesity and NIDDM promote the development of cardiovascular disease. In contrast to cardiovascular disease relatively little is known about the relationship between dietary fat and cancer. Nonetheless current dietary guidelines on fat intakes reflect what is understood about the prevention of cancer.

Obesity and NIDDM

Spiralling increases in the prevalence of obesity have been reported in Britain and the US over the past decade. In a recent review[3] outline how, in Britain, average fat intakes have been significantly increasing and physical activity levels have been significantly decreasing in the years when obesity prevalence was growing dramatically. Other experimental work supports the hypothesis that the interaction between a high fat diet and low physical activity levels may be a significant factor in the phenomenal increases in obesity prevalence observed in developed countries over recent years[4].

Strong support for the fattening effects of a high fat consumption is evident in the recent report from the Scottish Heart Study which included over 11,000 men and women[5]. This study found that the leanest adults used carbohydrate (including sugar) as a dietary energy source rather than fat

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while the opposite was true for the most obese adults; the leanest adults had the lowest intake of fat and the highest intake of carbohydrate (including sugars), while the most obese adults consumed the highest amount of fat and had the lowest intakes of carbohydrates. Many dietary studies have found that low fat intakes are usually associated with high sugar intakes and vice-versa. In fact this is often referred to as the fat-sugar see-saw. The inverse relationship between dietary intakes of fat and sugar suggest that recommendations which advise populations to reduce fat and sugar intakes simultaneously may be unrealistic.

The recent surge in incidence of NIDDM mirrors the trends in obesity discussed above and reflects the strong association of obesity and NIDDM. A recent report from the Centre for Diseases Control in Atlanta (Table 2) outlines the importance of obesity prevention (which emphasises a reduction in fat intakes) and increased physical activity to counteract these trends. The type of fat that should be eaten to minimise the atherogenic lipid profile associated with NIDDM are discussed in the section on PUFAn-3.

Table 2. **US diabetes cases at record level**

1980-1994:	+ 33% increase in blacks + 11% increase in whites
Risk factors:	older age, race, ethnicity, family history, obesity and physical inactivity

Cardiovascular Disease

Dietary fat mediates it's effects on cardiovascular disease through atherogenic and thrombogenic factors. Atherosclerosis is a long-term process beginning in teenage years. In general, the atherogenicity of dietary fat intakes can be assessed in terms of blood lipid concentrations which are an important focus for primary prevention programmes. Thrombosis is less well understood and although it is likely to be involved in the development of atherosclerosis, it is a much more acute process[6]. Anti-thrombogenic factors can, therefore, be much more effective in reducing the risk of acute events in cases where atherosclerosis is established, for example, middle-aged men in populations where cardiovascular disease is prevalent, or in secondary prevention (in patients with established cardiovascular disease). The latter was demonstrated clearly in the Diet and Reinfarction Trial where in men (n2033) post myocardial infarction who were randomised to receive the anti-thrombogenic diet therapy of PUFAn-3 (oily fish) were found after two years to have experienced a significant reduction in mortality compared with the group receiving anti-atherogenic intervention[7] (Table 3).

Table 3. **Effects of different dietary interventions on death and Ischaemic Heart Disease (IHD) event in men (n2033) post myocardial infarction**

Dietary advice	*RR* of death*	*RR of IHD event*
Fat	0.97	0.91
Fish	0.71**	0.84
Fibre	1.27	1.23

**RR- Relative risk* ***p<0.05*

The effects of the very strict NCEP Step 2 (Table 1) on the plasma lipoprotein profiles in 72 men and 48 women were recently reported from a meta-analysis of five previously published studies[8] and discussed in an editorial review[9]. There was a large variability found in the blood lipid response to this diet and this was found to be mainly due to genetic influences in men and age in both sexes. The environmental factors were as well controlled as possible in that all food and drink was provided during the study, body weight was stabilised, alcohol and vitamin supplements were excluded, subjects on lipid lowering medication, and those with disorder likely to affect results, were excluded. Age and genetic factors were able to explain 48% of the variance in Low density lipoprotein (LDL) response in men while age explained a corresponding 13% of the variance in women. The authors conclude that baseline LDL cholesterol concentrations, as a marker of genetic background, are the primary determinant of LDL response to an NCEP Step 2 diet in men. However, the decline in LDL cholesterol may be overestimated by predictive equations based on changing the dietary fat composition in men with low LDL cholesterol concentrations and may be underestimated in those with elevated levels. The determinant of variability of LDL response in women are less clear but age appears to play a role.

Individual Fatty Acids Vs. Major Classes of Fatty Acids

Considering that dietary guidelines on the type of fat should be eaten are issued in terms of the three major classes of fatty acids - SFA, MUFA and PUFA - the highly variable effects that individual fatty acids (even those within the same class) have on blood lipid concentrations may seem surprising. The changing emphasis from the major fatty acid classes to individual fatty acids is described very well by Kris-Etherton and Yu[10]. The variable effects of individual SFA, MUFA and PUFA on total blood cholesterol, LDL cholesterol and high density lipoprotein (HDL) cholesterol may be due to the potency of myristic acid at raising blood cholesterol levels which can be compared with the neutrality of stearic acid.

Considering unsaturated fatty acids: Although oleic acid (MUFA) has a neutral or mildly hypocholesterolaemic effect compared with the more potent hypocholesterolaemic effects of linoleic acid (PUFAn-6), nonetheless the beneficial effects of oleic acid on HDL cholesterol levels are likely to be clinically significant.

Trans Fatty Acids

A trans fatty acid occurs when the isomeric configuration of the hydrogen carbons at a double bond position are changed from the normal cis configuration - where both atoms are on the same side of the carbon chain - to the trans configuration where the atoms occur on different sides of the carbon chain. In the normal cis configuration there is a 'kink' in the molecule which does not allow the fatty acids to fit closely together - thus resulting in greater fluidity - and the fat will be liquid at room temperatures. The trans configuration results in straighter molecules which like SFA fit closely together and are solid at room temperature.

There are different dietary sources of trans fatty acids (Table 4). Some occur naturally in dairy foods and meat due to

the hydrogenation of palmitoleic and linoleic acid in the rumen of cattle by bacteria. This hydrogenation occurs at temperatures of 37°C in the presence of hydrochloric acid. The types of trans fatty acids produced from animal sources have been part of the human diet for generations

Table 4. **Relative risk of coronary heart disease (CHD) in 69,181 women relative to trans fatty acid intake**

	Quintiles of trans fatty acid intake				
	1	2	3	4	5
Total trans isomers	1.0	1.23	1.11	1.36	1.67*
Vegetable sources	1.0	1.43	1.11	1.39	1.78*
Animal sources	1.0	0.76	0.69	0.55	0.59

*$p<0.05$

Early this century the process of hydrogenating vegetable and marine oils to manufacture hard fats which are useful for the production of margarines, cakes and biscuits was started. This introduced a new range of trans fatty acids into the human diet. These vegetable and marine sources of trans fatty acids are produced by passing hydrogen gas over the oils at very high temperatures in the presence of a catalyst. The hydrogenation of double bonds occurs more randomly and there is also a tendency for positional isomerisation to occur (where the double bond migrates up or down the carbon chain). The variety of different isomers, both trans and positional, produced by this process is manifold. In the case of the highly unsaturated marine oils the majority of fatty acid isomers produced by hydrogenation remain unidentified.

Total dietary intakes of trans fatty acids have been declining in recent years particularly those of vegetable and marine origin. Currently average intakes of total trans fatty acids are estimated to contribute 2% of energy in the UK diet[1] and 2.6% of energy in the US diet. In the Gulf region intake of trans fatty acids are likely to be low and vegetable and marine sources of trans fatty acids would not be an issue for those following the traditional diet of the area.

Recently a large prospective study of coronary heart disease risk among women reported that the relative risk of developing heart disease was increased by 67% for women having the highest, compared to those having the lowest, intakes of total trans fatty acids. From food intake data this American study was able to determine that this risk was associated specifically with trans fatty acids from vegetable sources only (where the risk increase was 78%) and that there was no increased risk associated with the consumption of trans fatty acids from animal sources[11].

Another study provides further evidence of the negative effects of trans fatty acids where high dietary intakes (9% of energy intake) of elaidic acid (t18:1) was found to significantly elevate lipoprotein (a) (Lp(a)). Lp(a) is a lipoprotein that is associated with atherosclerosis and thrombosis and blood concentrations were previously understood to be wholly determined genetically[12]. However, the high intakes of elaidic acid (t18:1) used in the experimental diets (9% of dietary energy) are unlikely to occur in the diet under normal circumstances[12].

PUFAn-3

Oily fish is the main dietary source of PUFAn-3 fatty acids eicosapentaenoic acid (EPA;20:5) and docosahexaenoic acid (DHA;22:6). How ingestion of these fatty acids can invoke an anti-thrombogenic response is described by Simopoulos[13]. Dietary intakes of PUFAn-3 inhibit the production of PUFAn-6 (arachidonic acid: AA;20:4) from linoleic acid. EPA replaces AA in phospholipid membranes and competes with AA for enzymes to produce a different series of eicosanoids in plarelets and endothelial cells which have an anti-aggregatory effect. In addition EPA competes with AA and produces leukptrienes series 5 instead of the leuktrienes series 4 produced by AA. The balance is favour of leukptrienes series 5 has anti-inflammatory effects which may be significant for the management of chronic inflammatory disease such as arthritis and inflammatory bowel disease. Recently it has been postulated that leukoptrienes series 5 may be protective against cancer[14].

The balance between PUFAn-3 and PUFAn-6 have, therefore, important implications for health. It is a matter of concern that the dramatic changes in human fat intakes, which have occurred over the last 100 years or so, have resulted in a much higher ratio of PUFAn-6:PUFAn-3[13]. Considering the effects of PUFAn-3 this may be significant in relation to cardiovascular disease and cancer.

PUFAn-3, Hypertriacylglyceridaemia and NIDDM

Dietary intakes of PUFAn-3 have potent triacylglyceride (TAG) lowering effects and variable effects on LDL and HDL concentrations. With increasing dietary increments of EPA and DHA there is a corresponding decrease in blood concentrations of total TAG and of the main TAG carrying very low density lipoprotein (VLDL)[15]. This has clinical relevance for subjects at risk of hypertriglyceridaemia such as obese patients, patients with NIDDM and post-menopausal women for whom the combination of hypertriacyglyceridaemia with low HDL concentrations represents an atherogenic profile.

A recent post-prandial study of post-menopausal, non-diabetic women (n10) examined their response to the recommended low fat (25%) high carbohydrate (60%) NCEP step 2 diet compared with a high fat (45%) low carbohydrate diet (40%)[16]. These workers found that the low-fat, high-carbohydrate diet yielded a more atherogenic response in blood lipid concentrations. Furthermore this study also found that the low-fat, high carbohydrate diet had a more adverse effect on post-prandial insulin concentrations[16]. These findings question the wisdom of advising post-menopausal women to adopt very low fat diets. It also has implications for subjects with abnormal glucose control who tend to develop hypertriacylglyceridaemia.

A recent report from a large multi-centre study, which included over 400 male and female patients with NIDDM, suggests that PUFAn-3 given as a small daily dose of EPA and DHA (equivalent to a potion of oily fish)can be effective at ameliorating hypertriacylglyceridaemia without adversely affecting glycaemic control[17]. The TAG-lowering response was more significant in diabetics whose HDL levels were initially low. Previous studies have yielded inconsistent findings about the effects of PUFAn-3 on glycaemic control.

This recent study involved a 6 month follow-up period and the protocol did not allow any change in oral hypoglycaemic agents. The authors conclude from their findings that a moderate dose of PUFAn-3 can provide a suitable option for the management of patients with hypertriacylglyceridaemia including those who have abnormal glucose control[17].

Dietary Fat and Cancer

Investigating the relationship between dietary fat intakes and cancer is inherently difficult due to methodological problems. This review will outline the direction of current research on the role of dietary fat in relation to the cancers affecting the colon and the breast.

The association between meat intakes and incidence of colon cancer is apparent in international comparisons using data on per capita meat consumption[18]. However, there are many other differences between these countries besides their meat consumption pattern which may equally define their risk of colon cancer. Greeks, for example, enjoy high intakes of meat but have a low risk of developing colon cancer. Within high risk countries a high fat intake and a low consumption of fruit and vegetables are positively associated with risk of colon cancer which may be important risk factors associated with a high fat intake[18].

International cross-country comparisons show a similar positive association between fat intakes and the incidence of breast cancer. However this has not been shown in prospective studies: "in large prospective epidemiological studies, little evidence has been seen to support any major positive association between dietary fat and risk of breast cancer over the range of 15-45% or more of energy from fat"[19]. However recent studies indicate that individual fatty acids, rather than the total amount of fat or the major classes of fatty acids, may provide the key to how fat intakes may be associated with an increased risk of breast cancer[14]. There is no evidence to link intakes of saturated fatty acids as a class with breast cancer. While there is no evidence of a protective effect of MUFA per se, there have been a number of studies suggesting a protective effect of olive oil (higher socio-economic status of high olive oil consumers). Animal studies suggest that PUFAn-6 may have a carcinogenic effect while PUF An-3 may be protective due to the production of leukotrienes series 5. Finally, the Euramic study, which included adipose tissue biopsies found an increase in breast cancer risk associated with greatest stores of trans fatty acids.

CONCLUSION

A reduction in fat intakes combined with an increase in physical activity levels is recommended to reduce the increasing prevalence of obesity. While increased physical activity is known to be directly effective in reducing insulin resistance, a reduction in the prevalence obesity will have a 'knock-on lowering' effect on NIDDM incidence.

A moderate reduction in fat intakes diets combined with an increase in PUFAn-3 may reduce cardiovascular risk in subjects with hypertriacyglyceridaemia (patients who are obese or have NIDDM, and post-menopausal women). Intakes of individual fatty acids rather than of the major classes of fatty acids may be more critical in determining risk of cardiovascular disease. Intakes of individual fatty acids may explain the relationship between dietary fat and cancer.

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