CHOLESTEROL UPDATE 2001

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***Abstract*:** The traditional view of dietary cholesterol and fats on health has been narrowly focused on the effects of fatty acids, triacylglycerols of different sources, lipoproteins and selected dietary constituents. New directions are needed towards the understanding of the mechanisms leading to the known benefits and perceived risks (including those seen from epidemiological data) to cardiovascular disease. Studies need be directed beyond saturation/polyunsaturation of dietary fats and elevation/oxidation of low-density lipoprotein cholesterol so as to gain understanding of the metabolism of dietary fats/components, the roles of regulatory proteins and mechanisms of action whereby useful effects can be optimized or exploited in authentic healthy products to benefit consumers. Elevating HDL, optimizing postprandial lipoproteins and other lipids, reduction of endothelial dysfunction and appropriate application of antioxidants and other dietary constituents to maintain cardiovascular health are areas needing attention.

Introduction

It all began in the 30s when it was demonstrated that dietary cholesterol can cause arterial lesions in animals and later a diet-heart hypothesis emerged from epidemiological studies relating diet to heart disease. A large body of evidence supports a direct relationship between total serum cholesterol and the risk of coronary heart disease (CHD). This includes within-population studies and between-population studies.[1] And familial hypercholesterolemia, a genetic disorder characterized by high levels of LDL cholesterol, has an exceedingly high rate of premature atherosclerosis (clogging of arteries). Animals with both spontaneous and diet-induced hypercholesterolemia develop lesions similar to human atherosclerosis. Dietary fat, in particular high in cholesterol and saturated fat, was attributed to increase the likelihood of aetherosclerosis that in turn can lead to coronary artery disease (CAD) and possibly heart attack. While dietary fat intake-CHD risk hypothesis is attractive to explain epidemiological data, there were exceptions, e.g. Crete had the lowest CHD while Finland had the highest although both populations consumed approximately 40% of energy from fat. Studies on migrant groups[2] appear to support a causal relationship of saturated fat intake to CHD risk. Studies on total serum cholesterol to predict CHD risk were widespread especially with reference to the equations of Keys[3] and Hegsted.[4] While the equations were valid for total cholesterol predictions for saturated-polyunsaturated fats and cholesterol intake they are of questionable relevance in the prediction of CHD risk. Attention has since shifted to the importance of measuring the levels of "good" high density lipoprotein cholesterol (HDL), which removes cholesterol out of the peripheral blood vessels, "bad" low density lipoprotein (LDL) cholesterol, which delivers cholesterol to the peripheral blood vessels and other lipid parameters relevant to risk of CHD. LDL-cholesterol when oxidized (or chemically changed) starts a chain of events leading to atherosclerotic plaques, and other lipid parameters relevant to risk of CHD. Since HDL is strongly and inversely correlated to CHD risk, the ratio of total cholesterol to HDL is considered a better predictor of CHD risk than total cholesterol alone.[5]

While cardiovascular disease may be importantly diet related, the disease is actually multifaceted being influenced by physiology, genetics, environment and psychosocial stresses. Major identified risk factors for CHD include cigarette smoking, elevated blood pressure, elevated plasma cholesterol, obesity, diabetes and elevated blood triacylglycerols (TAG). Although cholesterol and saturated fats have been singled out to receive most attention, it is now recognized that the science of dietary fat is not as simple as has been assumed.[6] Analysis of the available epidemiological and clinical data indicates that for the general population, dietary cholesterol makes no contribution to atherosclerosis and risk of cardiovascular disease.[7] Many dietary recommendations have become questionable while others have not led to the desired results or even have given rise to undesirable problems. The limits set for "saturated" fats are of debatable benefit while their replacement with partially hydrogenated fats (containing *trans* fats) has increased health risks to unsuspecting consumers who assumed them to be "unsaturated or polyunsaturated" fats. Likewise the widespread advice to reduce fat intake for those consuming >35% of total calories as total fat, only encouraged a shift to high-carbohydrate diets which can turn out to be worse than high-fat diets. The disturbing result of a reduction of fat (not overall calories) intake has been the increase in obesity, an outcome arising from replacing fat calories with carbohydrates. It ought to be noted that such substitution also has the likelihood of stimulating hunger, leading to overeating. Further, sources of dietary protein, amounts and types of fatty acids, antioxidants and other dietary natural products are being examined for their effects on cardiovascular health. Increasing evidence have accumulated that the genesis of atherosclerosis is an inflammatory action on the endothelium and some polyunsaturated fatty acids, e.g. linoleic acid, may cause pronounced pro-inflammatory effects.

Reduction of dietary fat intake, contrary to previous views, had no effect on total mortality as can be seen from a review of 27 intervention trials.[8] It was noted that "despite decades of effort and many thousands of people randomized, there is still only limited and inconclusive evidence of the effects of modification of total, saturated, monounsaturated, or polyunsaturated fats on cardiovascular morbidity and mortality". In another study[9] many dietary fat recommendations were criticized to be scientifically unfounded; "mainstream nutritional science has demonized dietary fat, yet 50 years and hundreds of millions of dollars of research have failed to prove that eating a low-fat diet will help you live longer." Although it is recognised that modification of dietary fat intake can alter serum cholesterol levels, the efficacy of dietary changes compared to proven cholesterol-lowering drugs is questionable; "diet rarely drops LDL by more than 10%, which is effectively trivial for healthy individuals, although it may be worth the effort for those at high risk of heart disease whose cholesterol levels respond well to it." It is now recognized that elevated or too low cholesterol levels are health risks or such levels may be symptoms to many disease problems. Further, various lipoprotein cholesterol forms (HDL, LDL, VLDL, Lp(a), etc) play important roles in the utilization of cholesterol by the body while the progress to atherosclerosis can be modified by various factors including other types of dietary intakes (antioxidants, natural products, etc). Even as more becomes known we are still intrigued with the Eskimo and French paradoxes and remain limited with our ability to provide "perfect" guidelines for dietary fat intake.

Fatty Acids

Despite considerable research, the understanding of the effect of dietary fatty acids on the regulation of blood cholesterol levels has remained controversial mainly because of the influence of partisan groups supported by large dietary oils and fats producers. The earlier recommendations of reduction of saturated and polyunsaturated fats as distinct groups (rather than specific fatty acids) were only for practical reasons and not totally based on scientific evidence. Recommended proportions of saturates: monounsaturates: polyunsaturates as specified by several countries are in the range 1:1-1.7:0.6-1; the American Heart Association recommends the proportions 1:1:1. It is noted monounsaturated fatty acid is favoured over polyunsaturated fatty acids because of its oxidative stability and neutral (or slightly hypo-) cholesterolemic property. Similarly saturated fatty acids of medium chains are similarly favoured with the additional beneficial property of easier metabolism for energy. Oleic acid is favoured to replace certain polyunsaturated acids, e.g linoleic acid, because of oxidative stress, pro-inflammatory response and competition with ω3 very long chain polyunsaturated acid (LCPUFA) functions. Other detailed recommendations will have to take into account of (a) the nature and relative amounts of fatty acids of the fat and the natural fatty acid distribution of *Homo sapiens* (saturated ~ monounsaturated > polyunsaturated; 18:1 > 16:0 > 18:2~18:0~14:0 > 12:0 > 18:3), (b) adequate amounts of essential fatty acids, e.g. ω3 LCPUFAs, and (c) perhaps specific individual requirements.

Saturated fatty acids with short, medium, long and very long chains behave differently in their effects on blood cholesterol and similarly "polyunsaturated" acids (PUFAs, usually referring to 18:2 and 18:3 acids) have biological effects different from long chain polyunsaturated fatty acids usually of marine origin. The problem of the present developed and also developing societies' diets is the high dependence on processed oils that will of course only provide exaggerated amounts of fatty acids derived from the particular source (e.g. soya, palm, rapeseed, etc). Except for palm, olive and other high-oleic oils that need no hydrogenation for many applications, polyunsaturated oils are partially hydrogenated before use. The danger of *trans* fatty acids from partial hydrogenation of polyunsaturated fats has now been recognized as the major problem of many processed oils in wide supply.[10,11] Hydrogenation and thermal/chemical action on fats give rise to positional and geometrical isomers of unsaturated fatty acids, some of which interfere with metabolic pathways. Diets high in *trans* fatty acids not only elevate the "bad" LDL-cholesterol and lipoprotein-a [Lp(a)] but also depress the "good" HDL-cholesterol level, a situation which make their consumption a higher risk than most saturated fats.

The cholesterolemic effects of individual fatty acids have proven to be more difficult to determine precisely because of the difficulty of providing studies with adequate controls and the lack of understanding of the digestion, absorption and metabolism of various types of fats. A summary of data from a number of well-controlled studies[12-19] is shown in Table 1.

Experimental Results on Lipoprotein Effects by Fatty Acids

Many studies on the effect of specific fatty acids on blood lipids and lipoproteins in humans have provided many inconsistent results[4,6,10,12,18-24] A recent example on feeding adolescents with dairy-based saturated fatty acids including 12:0 and 14:0, which are normally cholesterolemic, showed an unexpected negative correlation to serum cholesterol.[22] In other cases conflicting data may arise if the dietary levels of the specific FA are insufficiently pronounced to cause differences to be observed as the body's metabolism rapidly reestablishes the usual distribution of FAs. Quantitation of the specific contributions of exogenous and endogenous FAs especially of C12-C18 FAs to lipid profiles is sometimes difficult and can be a source of complications. Furthermore, lipoprotein profiles are also affected by the amount of free cholesterol in the diet. The other obvious problem is that some researchers neglect the contribution of the structures of the TAGs and the positional differences (i.e. *sn*-1, *sn*-2 or *sn*-3) of

Table 1. Effect of fatty acids and other dietary components on blood lipids

Fatty Acid	Total C*	Notes*	CHD#
Caprylic & capric (8:0 &10:0)	+	Insufficient evidence; LDL ±; short- and MC-FAs are transported by the portal vein	
Lauric (12:0)	+	LDL ++; TAG ± ; InfR +?	
Myristic (14:0)	+++	LDL ++	
Palmitic (16:0)	+ or ±	LDL + or ± ; HDL +	±#
Stearic (18:0)	±	LDL ± ; HDL − ; Lp(a) + ; poorly absorbed	±#
Elaidic (*trans* 18:1)	+	LDL +; HDL −−, Lp(a) ++	++
Oleic (18:1)	−	LDL−; HDL ± ; TAG + ; InfR +; Factor VIIc +	−−
Linoleic (18:2 *n*-6)	−−	LDL−; HDL −; InfR +++	+or −#
α-Linolenic (18:3 *n*-3)	−−	LDL−; HDL −; TAG−; InfR +	−
Behenic (22:0)	+	HDL ±; TAG ±; very poorly digestable and absorbed	
EPA & DHA (20:5 *n*-3 & 22:6 *n*-3)	±	VLDL −; LDL +; HDL +; TAG −−−	−−−
Total fat	+	LDL +; HDL +; Factor VIIc +	±#
Cholesterol	+	LDL +; HDL −	+
Carbohydrate	+	LDL +; HDL −; TAG ++	+
Fibre	−	LDL −; HDL ±	−

*Changes of total C (total cholesterol) and LDL values caused by fatty acids are relative to stearic acid (18:0); +++> ++> + refers to relative levels of elevation; ± neutral; −−− > −− > − refers to relative degrees of depression; poor digestion and absorption refers to the 1,3-positional fatty acids under the action of pancreatic lipase. Carbohydrate can be metabolized to fats but importantly affects insulin levels. InfR = inflammatory response to endothelial cells. Factor VIIc is a measure of the activation of clotting.

Aspects of the effect of total dietary fats or individual fatty acids on risk to CHD can be controversial, − means reduction (beneficial), + means detrimental; indicated FAs in this column represent typical long chain saturated, polyunsaturated and *trans* FAs from hydrogenation of C18 FAs.

the contributing fatty acids. TAGs can be highly structured stereospecifically in naturally occurring oils and fats and the action of lipases is also highly 1,3-specific as well as selective to chain length and unsaturation. The rate of digestion (lipolysis), ease of absorption and reesterification of the resulting FFAs and 2-MAGs (2-monoacylglycerols) will have an important consequence on their subsequent metabolism, the blood lipid profiles and finally delivery to tissues. For example, a randomized, two-period, crossover design was used to compare the effects of replacing 17% of the 30-35% fat in the usual Australian diet (high in saturated dairy fats) with palmolein and olive oil (each oil at 17%) showed no significant difference in their effects on plasma lipids.[20] The high overall palmitic (33%) and total saturated FAs (45%) content of palmolein diet did not contribute to cholesterolemic effects compared to the olive oil diet (16% of 16:0 and 27% total SFAs). It is clear that the naturally structured TAGs of palmolein play a role in the observed beneficial results. Contradictory results on the effects of saturated fatty acids may come from experiments where extreme (>15% en) rather than moderate (5-10%) changes were made among different fatty acids. The cholesterolemic effects of saturated FAs can be more pronounced when high cholesterol intakes depress LDL receptor activity.[21]

Digestion, Absorption and Metabolism of Fats

Products of TAG hydrolysis by gastric and pancreatic coliphase-dependent lipases are free fatty acids FFAs and *sn*-2 MAGs. MCTAGs and TAGs containing 1,3-MCFAs can be partially hydrolysed by gastric lipases and completely by the pancreatic lipase in the small intestine while TAGs with long chain fatty acids mainly

by pancreatic lipase. Studies on the action of lingual, gastric and pancreatic lipases on structured and defined TAGs and the subsequent transport of the digested lipids to the lymph over a 24-h period revealed that a lot of observations are still not completely understood. For humans the gastric lipase can partially release medium chain FAs at the 3-position of TAGs under the relatively acidic conditions while the main digestion will have to be dependent on pancreatic lipase aided by bile acids and bile salts. MUFAs and PUFAs are readily absorbed after their release by the action of pancreatic lipase and bile salts emulsification. However, even after release, common saturated long chain FAs such as 16:0 and 18:0 seems to be relatively poorly absorbed because of their higher melting points and tendency to form less soluble soaps (of Ca and Mg) and hydrates at the pH of the small intestine. MCFAs, being relatively more hydrophilic than the LCSFAs, can be directly absorbed and are transported into the portal vein and hence to the liver where they are oxidized for energy. 2-MAGs are micellarized and absorbed more readily than the long chain FFAs. 2-MAGs are reesterified with FAs to TAGs and transported to the lymph by chylomicrons. The 2-positional FAs in chylomicron triacylglycerols after 4 h feeding remain closer to *sn*-2 FAs of feed material while after 8 h changes are seen in the TAGs which may involve the incorporation FAs from hepatic VLDL. Not much quantitative data however is known of the less slowly digested TAGs containing long chain saturated FAs at the 1,3-positions and their fate as a consequence of their much slower absorption.

Only recently[24-26] experiments have been designed to try to understand the digestion, absorption and metabolism of different dietary fats. Fatty acid chain length and unsaturation affect their degree and rate of digestion and absorption and subsequent metabolism. For example from lower postprandial lipid profiles there are indications that fats with 1,3-stearic and palmitic acids are more slowly digested and absorbed.[16,27]

Stearic acid-containing TAGs have attracted considerable attention because of their poor digestibility and absorption especially when stearic acid is at the 1,3-positions. The slower digestion and reduced (or slower) absorption and enhanced excretion are probably responsible for the widely observed neutral cholesterolemic effect of stearic acid.[17] Decreased calcium absorption[24,25] due to insoluble soap formation with stearic and palmitic acids also support the lower or delayed absorption (but not slower reesterification to chylomicron-TAGs) of these fatty acids with consequences on the postprandial lymph and plasma lipid profiles. The saturated behenic acid (22:0) is even more poorly absorbed (estimated ~30% in humans) and even then what is absorbed appears to be considerably degraded into shorter chain FAs and carbon dioxide.[15] Highly structured TAGs with long chain saturated fatty acids at the 1,3-positions will therefore be less bioavailable especially with diets high in minerals (Ca and Mg) and fibre. In the case of cocoa butter fats, even though significant absorption (or rather little excretion) of saturated fatty acids may be observed, any significant delay in absorption of the FFAs may mean that a large amount could not be reesterified with the easily absorbed 2-MAGs but instead either undergo either the glycerol-3-phosphate synthesis pathway or probably broken down for energy, a situation which may be reminiscent of dietary DAG oils currently used in the management of obesity. Only fatty acids at the *sn*-2 position seem to be rapidly absorbed (as 2-MAG) and can be reesterified with absorbed exogenous (or available endogenous) fatty acids so that 2-positional fatty acids of TAGs dominate the effects of dietary fats on blood lipid profiles. Fig. 1 displays the distribution of fatty acid classes in common dietary fats and shows many common oils and fats in the monounsaturated category, e.g. olive, palm and canola, having the *sn*-2 fatty acids mainly as MUFAs.

Pancreatic lipase is not only highly 1,3-specific but also selective to chain length, unsaturation and perhaps the triglyceride structure. *n*-3 LCPUFAs are of particular interest because of the beneficial effects of DHA (22:6 *n*-3) and EPA (20:5 *n*-3) and these fatty acids are best absorbed when at the 2-positions of structured TAGs containing medium chain FAs at the 1,3-positions. Even among the PUFAs and LCPUFAs pancreatic lipase discriminates against the longer chain length FAs.[26-28] Recent studies continue to be focused on the understanding of the metabolism of postprandial lipids.[29-32] There is increasing evidence that an elevated blood concentration of TAG-rich lipoproteins (TRLs) especially in the postprandial state, may be atherogenic. The positional distribution of FAs of the TAGs can cause differences to be observed especially in the delivery of specific fatty acids to endothelial cells but our complete understanding is still lacking. A key factor of postprandial lipid metabolism is the activity of lipoprotein lipase, which plays a role in the clearance of chylomicrons derived from dietary fat. FAs (by virtue of their saturation, chain length, unsaturation) affect lipoprotein lipase activity probably by a FA feedback system in which accumulated FAs obstructs lipoprotein lipase (LPL) action. In a feeding experiment involving breakfast and lunch using rape, sunflower and palm oils, it was found that the postprandial total TAGs were high for sunflower and rape (2.42 and 2.43 mmol/L, respectively) and less for palm oil (1.98 mmol/L) even though it was not considered statistically significant for the small sample of experiments.[27]

Chylomicron cholesterol has an inverse relationship with HDL-cholesterol due to the transfer of TAGs and cholesterol esters between each other leading to a detrimental loss of HDL while the excessive chylomicron remnants have been postulated to be able to cause endothelial dysfunction. The postprandial lipid response from the ingestion of milk-emulsified palm superolein and other TAG oils containing palmitic and oleic acids indicate differences in the digestion of the TAGs.[28-33] Postprandial lipid profiles over 0 - 8 h or longer provide small but observable differences in the absorption and clearance of TAGs containing stearic and palmitic acids in comparison to MUFAs and PUFAs.

With the limited experimental data available some preliminary observations have been made: the level of postprandial chylomicrons was greater from a linoleic-rich diet as compared to an oleic-rich diet; likewise postprandial chylomicrons were more elevated from a high oleic (sunflower oil) diet relative to another high oleic (but containing some palmitic acid; olive oil) diet; levels of postprandial chylomicrons appear relatively low from palm oil diets; TAGs containing oleic acid at the 1- or 3-positions were digested and transported faster than TAGs with palmitic acid at these positions; postprandial Factor VIIc, a measure of blood coagulant activity, is similar in palm and olive oil diets but higher in high-oleic sunflower oil diet. Although as yet not well researched on, hepatic VLDL seems to have preferential retention of unsaturated acids including ω3 LCPUFAs from consumed monounsaturated fats and it has been observed that the 2-positional stearic acid (but not oleic acid) not only retards the clearance of chylomicron remnants but also promotes platelet aggregation induced by thrombin and adenine 5-diphosphate.[24,26,29-32]

TAGs of chylomicrons were mainly derived as expected from the 2-MAG pathway but there are indications that the glycerol-3-phosphate pathway also contributes to a minor extent. The synthesis of TAGs by the latter pathway may be required from a lack of 2-MAGs and if there is a delayed absorption of saturated FFAs, otherwise the balance of the latter need to be broken down for energy, a situation which will be reminiscent of DAG oils now used in the management of obesity;[33,34] DAGs are also present in palm oil and palmolein but only at 5-7%.

Human endothelial cell function is affected by unsaturated fatty acids and linoleic acid has recently been identified to cause the highest pro-inflammatory effect (an early stage disturbance possibly leading to atherosclerosis).[36] Although the details have yet to be documented, in the subsequent metabolism of chylomicrons the TAGs will again have to be hydrolysed and the fatty acids finally delivered to the cells. The hydrolysis of lipoprotein TAGs appears not to be dependent of oleic acid versus stearic acid at the 2-position[33] but other fatty acid types need to be investigated especially as interest has also been on the nature and levels of circulating non-esterified FFAs. It is worthy to note that the nature of the fatty acids delivered can affect endothelial function, e.g. 18:2 (most inflammatory) > 18:3 *n*-3 > 18:1 > carbohydrate-derived FAs.[36] Curiously lauric acid (12:0) was also active but this could be due to the derived MAG metabolite. If inflammatory events are important it would therefore mean that an excessive intake of polyunsaturated oils usually high in 18:2 *n*-6 acid may not be desirable, in addition to the need to provide a good balance with other important but less readily available dietary *n*-3 long-chain polyunsaturated fatty acids. It is possible that control of inflammatory events and/or the participation of other important regulatory proteins, e.g. insulin, are important in the genesis of several disease states. Cholesterol ester transfer protein (CETP), which also affects lipoprotein metabolism, has also been receiving attention but most results remain ambiguous.

The positional distribution of saturated FAs in TAGs has also important consequences in experimental atherosclerosis observed in animals.[37-40] It is well known that palm oil with saturated fatty acids positioned at the 1,3-positions of the TAGs is less atherogenic than the interesterified oil or lard which has a similar degree of unsaturation but has palmitic acid mainly at the 2-position. The experiments of Hornstra *et al*[37] indicated that palm oil has very low atherogenicity comparable to polyunsaturated oils and is even better than olive oil.[40] Virgin or red palm oil has even lower atherogenic properties[38] presumably due to added effects from antioxidants (tocotrienols, tocopherol, carotenes, etc) which are important to protect LDL from oxidation[41] and formation of atherosclerotic plaques.

Applications of Structured TAGs

MCTAGs have been available for some time and are well known for their digestability, easy absorption and use for rapid energy expenditure. Structured TAGs can be used for efficient delivery of desired fatty acids (e.g. DHA and EPA).[42] Structured TAGs can have MC FAs at the 1,3-positions while the 2-positions can be occupied by DHA (22:6 *n*-3) a valuable essential fatty acid. Similarly in cases of fat malabsorption structured TAGs with the incorporation of MC FAs at the 1 and/or 3-positions would be beneficial. For infant formula it may be desirable to have 2-positional palmitic acid, e.g. 18:1/16:0/18:1. New cocoa butter equivalents with reduced caloric values or even reduced levels of postprandial lipids can be possible with designed TAGs having1,3-positions occupied by 22:0 (behenic acid or other very LCSFA) or just stearic acid, taking advantage of their poor digestion and absorption, and a short chain FA at the 2-position. There appears to be good potential for designing TAGs as functional fats.

Guidelines to Moderate Fat Intake

The consumption of fat has dropped in developed countries, but still mostly to around 90 to 140 g per person daily while less developed countries is around 30-60 g; Japan is an exception at 24 g. Due to the effect of the media (especially in N. America) most of the saturated fats eaten are now limited to meat and dairy fats even though moderate intakes of these cause only small changes in serum lipids and are not considered a risk to CHD[7] for healthy individuals. However with the widespread appearance of *trans*-fats and also potential problems with polyunsaturated fats, there needs to be more emphasis on monounsaturated fats or more natural fats even if they are saturated and/or of dairy/vegetable origin.[43,44] MUFA oils remain preferable because of favourable cholesterolemic effects as well as high oxidative stability (practically comparable to SFA oils) as opposed to polyunsaturates. In view of the earlier discussions on triglyceride structure, Fig. 1 provides a good overview of oils and fats with MUFA properties. It should be noted that it may be preferable to minimize the

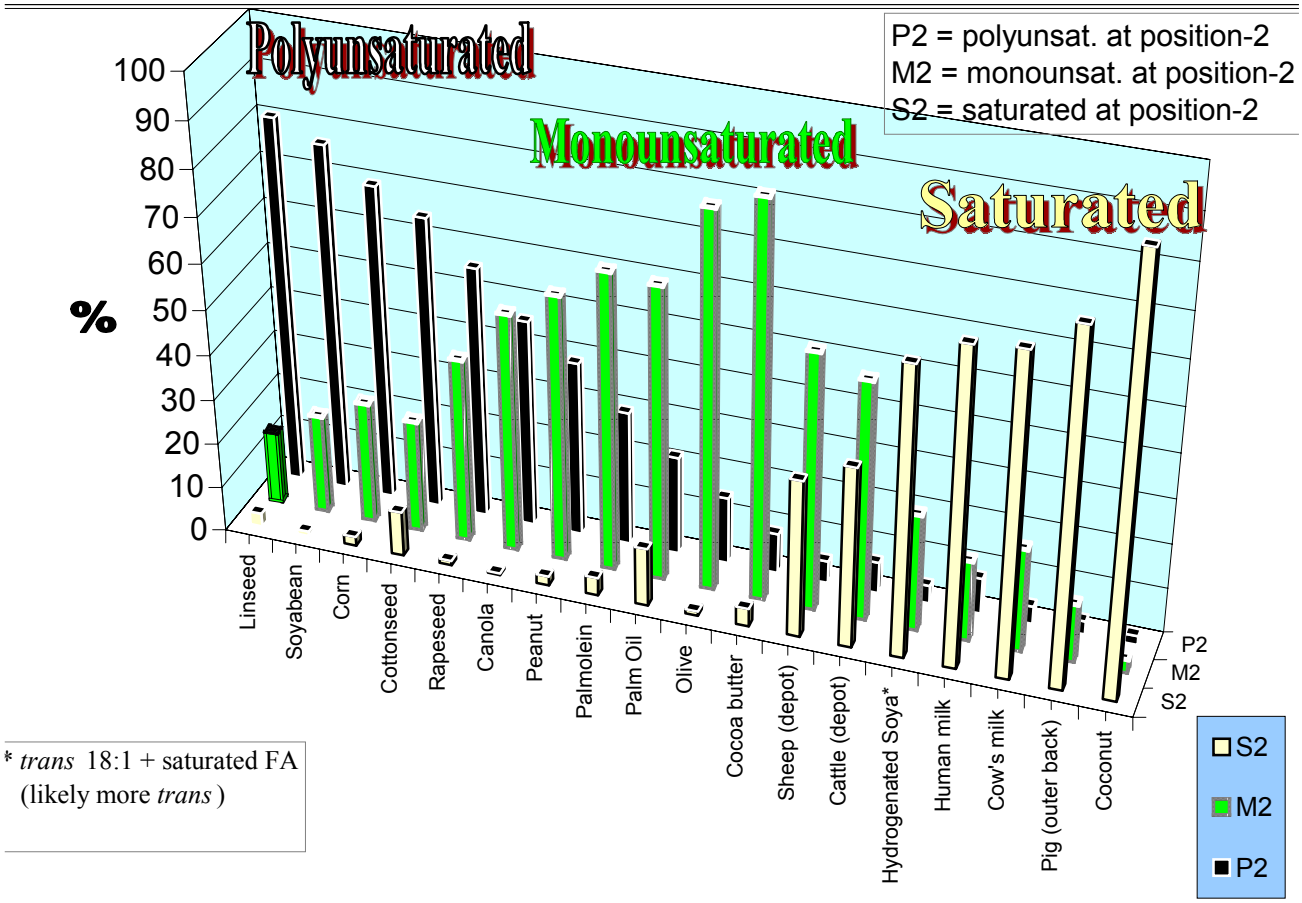

Figure 1. 2-Positional Unsaturation of Oils and Fats

lowering of HDL cholesterol while trying to reduce animal/dairy-based saturated fats with MUFA fats rather than with PUFA fats since the ratio of total cholesterol to HDL cholesterol (rather than either total cholesterol or LDL cholesterol alone) appears to be a better predictor of risk to CHD.[5-7,44] It may also be pointed out that the voluminous data from various studies do not support the strong association between intake of saturated fat and risk of coronary heart disease.[8-11,43-45] Low fibre not high SFA is the probable cause of high risk. Diets high in *n*-3 (or ω3) LCPUFAs of marine origin, however, are consistently associated with reduced risk of CHD and this has been the current explanation for the Eskimo paradox.

Any guideline to dietary fat intake has to depend on the available local supplies of oils and fats, bearing in mind that the endogenous fatty distribution is a mixture of mainly 18:1, 16:0, 18:2, 14:0 and 12:0 and minor amounts of LCPUFAs; too much deviation from the body's natural requirements will impose unnecessary stress on the organism which has to metabolize different or excessive amounts of certain acids. Moderate, not low, consumption of most dietary fats is beneficial while excessive consumption of only a single type of fat may not be desirable. While a balanced "30% saturated" fat and cholesterol intake in moderation (<1g/kg and <300 mg respectively) may not affect most healthy people, it is noted that a few individuals may respond unfavorably to a diet moderately high in cholesterol or some saturated fats (or both). Reduced intake of linoleic-rich oils, e.g. corn, sunflower, etc, if they are widely used, may be prudent in view of the high pro-inflammatory effect of linoleic acid and there is the need to balance it by an increased intake of ω3 oils.

In view of the Mediterranean experience and also the French paradox (low CHD from a diet high in saturated fats but not partially hydrogenated fats), it may be beneficial to have sufficient intakes of ω3 marine oils, vegetables and fruits of low caloric value, presumably to provide vitamins, antioxidants, phytosterols, fibre and minerals (e.g. Ca and Mg), and if red wine is included, more antioxidants. Consumption of high fibre in particular has consistently been shown to be beneficial[43-45] and may be caused by its ability to make fats less bioavailable. Greater benefits seem also to accrue for the prevention of both coronary heart disease and stroke by ensuring that the diet contains *n*-3 LCPUFAs (e.g. from marine fish) apart from a substantial amount of whole grain cereals, fresh vegetables and fruits.[44-45] Vegetables not only supply fibre and minerals but also antioxidants, phytosterols, small amounts of *n*-3 oils and some beneficial natural

products. Phytosterols and polar antioxidant natural compounds solubilize in DAGs better than TAGs, and will have beneficial effects on serum cholesterol.[43] Palmolein and superolein, it may be noted, can contain 5-7% of DAGs, constituents that are also known to reduce hypertriglyeridemia;[34,35] DAG oils from Japan are now being used for the management of obesity and atherosclerosis.

Marine fish is of course the main source of LCPUFAs and almost all studies have shown their beneficial effects against CHD and the risk of sudden cardiac death and protection against abnormal cardiac rhythms; low doses of *n*-3 LCPUFAs are protective irrespective of the amounts of total fat intake.[47] EPA and DHA as supplements are also effective. α-Linolenic acid (18:3 *n*-3) or ALA is not a good substitute for LCPUFAs (especially if they are of greatest need as for infants) as ALA, if taken in small amounts, has to compete with 18:2 *n*-6 and 18:1 for desaturation/chain elongation pathways in humans, so that conversion to EPA and DHA becomes inefficient.[47-8] With sufficient *n*-3 LCPUFAs and a balanced diet, *n*-6/*n*-3 ratios are likely to fall in the range 6:1 to 10:1 although it is still uncertain if this range can be taken as a recommendation.

Diet guidelines are difficult to provide as they must reflect the awareness that there are differences in genetic and metabolic makeup of people and adjustments need to be made so that they are also optimal for individuals. A healthy moderate (<30% en) fat diet (for >2-y olds) can be one with MUFA properties and high in antioxidants, low in cholesterol, *trans* fats and some hypercholesterolemic saturated oils, and low-to-moderate in linoleic-rich oils with a good balance of ω3 LCPUFA oils. Good intakes of low calorie fruits/vegetables and whole grain products or fibre but only moderate intakes of sugar, sodium salt and alcohol are also included in general recommendations for healthy diets. Other non-diet recommendations for reducing risk of CHD include achieving or maintaining healthy body-weight, increasing physical activity and avoidance of smoking and other environmental hazards. With a moderate and balanced fat intake and a healthy overall diet it is expected that at least for healthy individuals there will be less fear of cholesterol and "saturated" fat even as new "healthy" fat products appear in the market place

References

1. Keys A (1980) Seven countries: A multivariate analysis of death and coronary heart disease. Harvard University Press, Cambridge, MA.
2. Kato H, Tillotson J, Nichaman MZ, Rhoads GG, Hamilton HB (1973) Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: serum lipids and diet *Am J Epidemiology* 97:372-85.
3. Keys A (1984) Serum-cholesterol response to dietary cholesterol *Am J Clin Nutr* 40:351-59.
4. Hegsted DM (1986) Serum-cholesterol response to dietary cholesterol: a reevaluation *Am J Clin Nutr* 44:299-305.
5. Mensink RP, Katan MB (1992) Effect of dietary fatty acids on serum lipids and lipoproteins:a meta-analysis of 27 trials *Arteriosclerosis and Thrombosis* 12:911-19.
6. Willett WC (1997) Dietary fats and non-communicable diseases In: Shetty PS, McPherson K (eds) Diet, nutrition and chronic disease: Lessons from contrasting worlds Wiley, Chap 5.
7. McNamara DJ (2000) Dietary cholesterol and atherosclerosis *BBA – Mol & Cell Biol Lipids* 1529:310-20.
8. Hooper L, Summerbell, CD, Higgins JPT, Thompson RL, Capps NE, Smith GD, Riemersma RA, Ebrahim S (2001) Dietary fat intake and prevention of cardiovascular disease: systematic review. *BMJ* 322:757-763.
9. Taubes G (2001) The soft science of dietary fat. *Science* 291:2536-2545.
10. Mesink RP, Katan MB (1990) Effect of dietary *trans* fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects *New Eng J Me*d 323:439-445.
11. Willet WC, StampferMJ, Manson JE, Colditz GA, Speizer FE, Rosner BA, Sampson La and Hennekens CH (1993) Intake of *trans* fatty acid margarine, and risk of coronary heart disease among women *Lancet* 341:581-585.
12. Kris-Etherton M, Yu S (1997) Individual fatty acid effects on plasma lipids and lipoproteins: human studies *Am J Cliin Nut* 65:1628S-44S.
13. Harris WS (1997) n-3 Fatty acids and serum lipoproteins: human studies *Am J Clin Nutr* 65:1645S-54S.
14. Schaefer EJ (1997) Effects of dietary fatty acids on lipoproteins and cardiovascular disease risk: summary *Am J Clin Nutr* 65:1655S-56S
15. Cater NB, Denke MA (2001) Behenic acid is a cholesterol-raising saturated fatty acid in humans *Am J Clin Nutr* 73:41-4.
16. Tholstrup T, Sandstrom, B, Bysted, A, Holmer G (2001) Effect of 6 dietary fatty acids on the postprandial lipid profile, plasma fatty acids, lipoprotein lipase, and cholesterol ester transfer activities in healthy young men *Am J Clin Nutr* 73:198-208.
17. Dougherty, RM, Allman MA, Iacono JM (2001) Effects of diets containing high and low amount of stearic acid on plasma lipoprotein fractions and fecal fatty acid excretion of men *Am J Clin Nutr* 61:1120-8.
18. De Roos NM, Schouten EG, Katan MB (2001) Consumption of a solid fat rich in lauric acid results in a more favorable serum lipid profile in healthy men and women than consumption of a solid fat rich in trans-fatty acids *J Nutr* 131:242-45.
19. Gupta SV, Khosla P (2001) Palmitic and stearic acids similarly affect plasma lipoprotein metabolism

in Cynomolgus monkeys fed diets with adequate levels of linoleic acid *J Nutr* 131:2115-20.
20. Choudhury N, Tan L, Truswell AS (1995) Comparison of palmolein and olive oil: effects on plasma lipids and vitamin E in young adults *Am J Clin Nutr* 61:1043-51
21. Khosla P, Hayes KC (1993) Dietary palmitic acid raises plasma LDL cholesterol relative to oleic acid only at a high intake of cholesterol *Biochem Biophys Acta* 1210:13-22.
22. Samuelson G, Bratteby L-E, Mohsen R, Vessby B (2001) Dietary fat intake in healthy adolescents: inverse relationships between the estimated intake of saturated fatty acids and serum cholesterol *Brit J Nutr* 85:333-41.
23. Bautista LE, Herran OF, Serrano C (2001) Effects of palm oil and dietary cholesterol and plasma lipoproteins: results from a dietary crossover trial in free-living subjects *Euro J Clin Nutr* 55:748-54.
24. (a) Bergstedt SE, Hayashi H, Kritchevsky D, Tso P (1990) A comparison of absorption of glycerol tristearate and glycerol trioleate by rat small intestine *Am J Physiol 259 (Gastrointest Liver Physiol 22)*:G386-G393; (b) Renaud SC, Ruf JC, Petithory D (1995) *J Nutr* 125:229-237.
25. Moya M, Cortes E, Juste M De Dios MJ, Vera A (2001) Fatty acid absorption in preterms on formulas with and without long-chain polyunsaturated fatty acids in terms on formulas without these added *Euro J Nutr* 55:755-62.
26. Christensen MS, Hoy C-E, Becker CC, Redgrave TG (1995) Intestinal absorption and lymphatic transport of eicosapentaenoic (EPA), docosahexaenoic (DHA), and decanoic acids: dependence on intramolecular triacylglycerol structure. *Am J Clin Nutr* 61:56-61.
27. Pedersen A, Marckmann P, Sandstrom B (1999) Postprandial lipoprotein, glucose and insulin responses after two consecutive meals containing rapeseed oil, sunflower oil or palm oil with or without glucose at the first meal. *Brit J Nutr* 82:97-104.
28. Shahkhalili Y, Duruz E, Acheson K (2000) Digestibility of cocoa butter from chocolate in humans: a comparison with corn oil *Euro J Clin Nutr* 54:120-25.
29. Yli-Jokipii Y, Kallio H, Schwab U, Mykkanen H, Kurvinen J-P, Savolainen MJ, Tahvonen R (2001) Effects of palm oil and transesterified palm oil on chylomicron and VLDL triacylglycerol structures and postprandrial lipid response. *J Lipid Res* 42:1618-25.
30. Abia R, Pacheco YM, Perona JS, Montero E, Muriana FJG, Ruiz-Gutierrez V (2001) The metabolic availability of dietary triacylglycerols from two high oleic oils during the postprandial period does not depend on the amount of oleic acid ingested by healthy men. *J Nutr* 131:59-65.
31. Aoe S, Yamamura J-I, Matsuyama H, Hase M, Shiota M, Miura S (1997) The positional distribution of dioleoyl-palmitoyl glycerol influences lymph chylomicron transport, composition and size in rats. *J Nutr* 127:1269-73.
32. Redgrave TG, Kodali DR, Small DM (1988) The effect of triacyl-*sn*-glycerol structure on the metabolism of chylomicrons and triacylglycerol-rich emulsions in the rat. *J Biol Chem* 263:5118-23.
33. Summers LKM, Fielding BA, Herd SL, Ilic V, Clark ML, Quinlan PT, Frayn KN (1999) Use of structured triacylglycerols containing predominantly and oleic acids to probe early events in metabolic processing of dietary fat *J Lipid Res* 40:1890-98.
34. Gee PT, Goh SH (2000) Dietary and chiral diacyglycerols *Malaysian Oil Science and Technology* 10:49-50.
35. Taguchi H, Nagan T, Watanabe H, Onizawa K, Matsuo N, Tokimitsu I, Itakura H (2001) Energy value and digestibility of dietary oil containing mainly 1,3-diacylglycerol are similar to those of triacylglycerol (2001) *Lipids* 36:379-82.
36. Ong PJL, Dean TS, Hayward CS, Monica PLD, Sanders TAB, Collins P (1999) Effect of fat and carbohydrate consumption on endothelial function *The Lancet* 354:2134. [Added in proof] Toborek M, Lee YW, Garrido R, Kaiser S, Hennig B (2002) Unsaturated fatty acids selectively induce an inflammatory environment in human endothelial cells. *Am J Clin Nutr* 75:119-25.
37. Hornstra G, Lussenburg RN (1975) Relationship between type of dietary fatty acids and arterial thrombosis tendency in rats. *Atherosclerosis* 22:499-516.
38. Kritchevsky D, Tepper SA, Chen SC, Meijer (1996) Influence of triglyceride structure on experimental atherosclerosis in rabbits. *FASEB J* 10:A187.
39. Kritchevsky D (2000) Impact of red palm oil on human nutrition and health. *Food Nutr Bull* 21:182-188.
40. Goh SH (1999) Cholesterol, *Malaysian Oil Science and Technology* 8(2):58-59.
41. Yap SY, Choo YM, Hew NF, Yap SF, Khor HT, Ong ASH, Goh SH (1995) Oxidative stability of low density lipoprotein from rabbits fed atherogenic diets containing coconut, palm and soybean oils *Lipids* 30:1145-50.
42. Tsuji H, Kasai M, Takeuchi H, Nakamura M, Okazaki M, Kondo K (2001) Structured TAGs can have MC FAs at the 1,3-positions while the 2-positions can be occupied by DHA (22:6 n-3) a valuable essential fatty acid. *J Nutr* 131:2853-59.
43. Hodson L, Skeaff CM, Chisholm W-AH (2001). The effect of replacing dietary saturated fat with polyunsaturated or monounsaturated fat on plasma lipids in free-living young adults. *Euro J Clin Nutri* 5:908-15.
44. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer, M, Willett WC (1996). Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *BMJ* 313:84-90.

45. Simopoulos AP (2001). The Mediterranean Diets: What is so special about the diet of Greece? The scientific evidence. *J Nutr* 131:3065S-3073S.
46. Meguro S, Higashi K, Hase T, Honda Y, Otsuka A, Tokimitsu, Itakura H (2001). Solubilizaton of phytosterols in diacylglycerol versus triacylglycerol improves the serum cholesterol-lowering effect. *Eur J Clin Nutr* 55: 513-17.
47. Dewailly E, Blanchet C, Lemieux S, Sauve L, Gingras S, Ayotte P, Holub BJ (2001). *n*-3 Fatty acids and cardiovascular disease risk factors among Inuit of Nunavik. *Am J Clin Nutr* 74:464-73
48. Oomen CM, Ocke MC, Feskens EJM, Kok FJ, Kromhout D. α-Linolenic acid intake is not beneficially associated with 10-y risk of coronary artery disease incidence: the Zutphen Elderly Study. *Am J Clin Nutr* 74:457-63.

Glossary

CAD	Coronary artery disease
CETP	Cholesterol ester transfer protein
CHD	Coronary heart disease
DAG	Diacylglycerol or diglyceride
DHA	Docosahexaenoic acid; 22:6 *n*-3; *n*-3 = ω3
EPA	Eicosapentaenoic acid; 20:5 *n*-3; *n*-3 = ω3
Factor VIIc	A measure of coagulant activity (clotting); sunflower oil and butter diets increase Factor VIIc (postprandial) relative to palm oil or olive oil
FFA	Free fatty acid
FA	Fatty acid
HDL	High density lipoprotein, the "good" cholesterol
InFR	Inflammatory response, may cause endothelial dysfunction and progress to atheroscelerosis
L, O, P, S	Abbreviations for linoleic, oleic, palmitic and stearic acids respectively
LCPUFA	Long (or very long) chain polyunsaturated fatty acid, e.g. 20:5 and 22:6, *n*-3 = ω3
LCSFA	Long chain saturated fatty acid, e.g. 18:0
LDL	Low density lipoprotein, the "bad" cholesterol
Lp(a)	Lipoprotein (a), an atherogenic lipoprotein
LPL	Lipoprotein lipase
MAG	Monoacylglycerol
MCFA	Medium chain fatty acid, e.g. 10:0
MCT	Medium chain triacylglycerol
MCTAG	MCT
MUFA	Monounsaturated fatty acid, usually 18:1
NEFA	Non-esterified fatty acids or FFA
POP	TAG with palmitic, oleic and palmitic acids at *sn*1, *sn*2 and *sn*3 positions respectively
Postprandial	Immediately after a meal
PUFA	Polyunsaturated fatty acid, e.g. 18:2 and 18:3
SFA	Saturated fatty acid, e.g. 12:0 - 18:0
SOS	Triacylglycerol with stearic, oleic and stearic acids at *sn*1, *sn*2 and *sn*3 positions respectively
TAG	Triacylglycerol
TRL	Triacyglycerol rich lipoprotein
VLDL	Very low density lipoproteins

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