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INTRODUCTION

The specific dietary patterns of a population have a major influence on the prevalence and incidence of atherosclerotic vascular disease. This particularly manifests as the coronary heart disease (CHD) morbidity and mortality rates in various geographical regions. High consumption of saturated fats, cholesterol and energy are associated with higher blood cholesterol and higher frequency of myocardial infarction and death from CHD (1). The discovery of the low density

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lipoprotein (LDL) receptor and the subsequent elucidation of its mode of action in
the cell and in the body have provided a conceptual framework for understanding
the mechanisms that control the concentration of the most abundant cholesterol-
carrying lipoprotein in human blood (2). In tissue culture cells, the LDL receptor
and the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA
reductase) are both subject to end-product feedback regulation by cholesterol.
When cellular cholesterol levels rise, the synthesis of HMG-CoA reductase and
the synthesis of LDL receptors are suppressed. On the other hand, when cells
have an increased demand for cholesterol, the production of LDL receptors and
HMG-CoA reductase increases (3). The dietary cholesterol inhibits cholesterol
synthesis mainly in the liver and small intestines and this inhibition contributes
to maintenance of blood cholesterol at constant levels in healthy persons.
Human trials and animal studies confirmed the relationship of dietary saturated
fats and cholesterol intake to blood cholesterol and subsequently CHD.
Prevention of clinically manifested CHD and increase in healthful longevity are
the long-term goals, but controlling other parameters such as blood plasma
cholesterol, blood pressure and excess body weight, are very beneficial. Given the
strong causal relationship with CHD, changes in these parameters in an
individual or in a group of individuals, are quite acceptable endpoints of dietary
therapy (4,5). It is possible that fatty acids and some other components express
their effect at the level of the arterial wall to enhance the development of
atherosclerosis. The possibility that certain dietary fats are uniquely atherogenic
is intriguing, but to date their is no evidence to show that all dietary fats and oils
are directly atherogenic independent of the effect on lipoprotein metabolism.
Although it has been generally believed that high intakes of fats raise the
cholesterol level, a major nutritional discovery has been the finding that not all
the components of dietary fats have the same effects on cholesterol levels (6).
Dietary fat consists of triglycerides which contain fatty acids of three types —
saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA), and
each type of fatty acids appears to have different effects on cholesterol levels. In
general, their effects on cholesterol levels are similar to those on LDL, but they
can affect also other lipoproteins. Thus, each category of fatty acids should be
considered separately.

Dietary Cholesterol

There is perhaps some confusion between the importance of the cholesterol
content of the blood and that of the cholesterol content of the diet. The available
evidence strongly suggests that, for most people, dietary cholesterol has much influence on blood cholesterol concentration (6,7). The CHD mortality and the serum cholesterol have been closely correlated with the SFA intake. The diet heart feasibility study in the 1960s also gave very useful information about changes in blood cholesterol when dietary SFA content was altered. Vegetarians eat virtually no cholesterol and enjoy considerably lower LDL cholesterol (LDL-C) than age-matched meat eaters (8). There seems to be no requirement whatever for dietary cholesterol and the body synthesizes more than it needs each day. Thus a very sensitive balance is maintained and any excess dietary intake leads to accumulation in the blood and subsequently deposition and atherosclerosis (9-11). There is a consensus among epidemiologists that reduction of dietary cholesterol to below 300 mg/day induces a significant decline in the CHD risk for an individual. However, a more drastic restriction to approximately 200 mg/day total dietary cholesterol in moderate or high risk individuals can be extremely beneficial and may remarkably reduce CHD risk in these individuals (1,4,5).

Fibers

Plants contain a large number of polymeric substances, primarily carbohydrate in nature of two types — those polymers which dissolve in water, often forming gels (soluble fiber) and those which rapidly settle to the bottom (insoluble fiber). Wheat bran is rich in insoluble fiber with virtually no soluble fiber whereas the fiber in psyllium seeds is approximately 80% soluble. An anticarcinogenic action of insoluble fiber has been already known. The soluble fibers lower LDL-C significantly. Controlled clinical studies with soluble fiber at doses of 10 to 20 g/day have shown reductions in LDL-C of 20% or more. Fiber is considered to lower the serum cholesterol level by inhibiting the intestinal absorption of cholesterol and bile acid. These recommendations provide excellent benefits to human health, including protection against important degenerative diseases such as CHD, diabetes mellitus, and large bowel cancer (1,12-14).

Fatty Acids

Fat droplets in the cytosol, mostly triglycerides and phosphoglycerides of the plasma membrane, are the main intracellular sources of fatty acids. These fatty acids are released by the action of intracellular lipases and phospholipases. The fatty acids that are oxidized in mammalian tissues are either taken up from the blood or obtained by the hydrolysis of intracellular lipids. Plasma lipoproteins contain triglycerides that may be digested by lipoprotein lipase
before entering the cells. Free fatty acids in the plasma are bound to albumin and are easily taken up by the cells of most tissues.

SFAs — There is clear evidence showing that fats rich in SFAs will raise the blood cholesterol levels when they are substituted for carbohydrates in the diet. The SFAs such as lauric (12:0), myristic (14:0) and palmitic (16:0) acids have sizable effects on raising blood cholesterol, through raising the level of the LDL-C (15,16). Although this effect has been observed in comparison of populations and confirmed by animal and human intervention studies, the actual mechanism of action of SFAs in raising LDL-C is still not well understood. The most frequently observed measurably physiological change is a slowing in the clearance of LDL from the blood stream, but there is some evidence showing that LDL synthesis may also be reduced in some individuals (17,18). Since most LDL is normally removed from the plasma space by the liver through specific cell surface-receptor mechanisms (19), the number or the rate of functioning of this receptor has been the subject of investigation. SFAs of less than 12 carbon units do not raise blood cholesterol (20). Stearic acid (18:0) does not increase plasma LDL either in human or animal studies (21). There is strong experimental evidence that this fatty acid is rapidly desaturated between the ninth and tenth carbons as counted from the terminal methyl carbon at the “omega” end of the molecule (22). The product of this reaction is oleic acid (18:1 n-9), the most common monounsaturated fatty acid. Oleic acid has no significant effect in changing LDL-C (23). Saturated animal fats containing stearic acid would be expected to have less impact on LDL levels due to this effect. Populations around the Mediterranean, on Crete and Corfu take 10% or less of energy from SFAs and some Japanese in fishing villages consume even less (3 to 4% of energy intake), from this source.

PUFAs — They have two or more double bonds in their molecules. They are classified by the position of the first double-bounded carbon atom, at the third or sixth position from the terminal (omega) methyl group. Thus, they are designated as n-3 or n-6 fatty acids.

n-6 Fatty Acids — They are not synthesized in the body but play essential roles in cell structure and prostaglandins (24). In general, the need is met if the intake is 1-2% of energy. However, the increasing consumption of linoleic acid (the predominant n-6 fatty acid) has raised this percentage to about 2 to 7% of total energy. There has been a considerably diverse opinion about the beneficial effects of increasing the intake of n-6 fatty acids over the years (24,25). Total plasma cholesterol falls more when PUFAs are replaced with SFA, more than
when either MUFAs or carbohydrates are substituted. Comprehensive studies correlated dietary habits of high intake of linoleic acid with lower rates of vascular diseases (25).

n-3 Fatty Acids — They are also essential components of the diet and are found concentrated in certain tissues such as the testis, retina, and the central nervous system (26). Deficiency states have not been reported, therefore it is assumed that the daily requirement is quite small. The largest benefit of these fatty acids was confirmed by the reports that populations eating diets relatively high in marine oils have very low rates of CHD (27-29). Additionally, reduced platelet aggregation in patients and animals given fish oils or extracts have increased the need of further studies (30). Recently, reported decreases in triglyceride values in hypertriglyceridemic patients have supported their additionally beneficial effects (31). Epidemiological studies have suggested that fish consumption (mainly n-3 fatty acid ingestion) has a great effect on reducing the incidence of CHD at low as well at high levels of intake (32). The complex effect of n-3 fatty acids on lipoprotein metabolism needs to be assessed in terms of their relation to the level of intake and the contribution of other protective mechanisms such as altered eicosanoid metabolism. All PUFAs, including the essential fatty acids, are thought to have a blood cholesterol-lowering effect when taken in the diet. All PUFAs are assumed to have a hypolipidemic effect. A higher ratio of PUFAs (P/S ratio) is recommended for prevention of cardiovascular diseases (33,34).

MUFAs — If one recognizes the importance of controlling energy intake and limits all fats accordingly, monounsaturates appear relatively benign as a dietary component. They occur abundantly in nuts, olives and meats. In fact, when saturated animal fats are restricted, MUFAs tend to fall commensurately. There seems little reason not to allow those to be replaced in the form of vegetable oils. Diets containing 15 to 20% of energy from MUFA seem quite healthful on Crete and Corfu where CHD is relatively infrequent (35). There has been much recent interest in the observation that HDL cholesterol (HDL-C) remains higher when SFAs are replaced with MUFAs as opposed to the reduction in HDL-C values observed when either carbohydrates or n-6 PUFAs are used as substitutes (36-38). However, it should be noted that most studies of lipoprotein levels in populations eating low saturated fats have shown that they have lower HDL-C levels and very low incidence of CHD.

Trans Fatty Acids (TFAs) — These are unsaturated fatty acids (often monounsaturated) that have one or more of the unsaturated bonds in the less-
usual trans geometry. More commonly, these bonds have the so-called cis geometry that leads to a sharp bend in the fatty acid chain. TFAs occur in the fats of ruminants such as cows or sheep and arise from a hydrogenation process in the animal’s rumen. The main TFA is elaidic acid or trans-oleic acid (Trans 18:1) and is generated during hydrogenation of linoleic acid. Many “cholesterol-free” foods contain high levels of hydrogenated vegetable oils. The commercial process of hydrogenation convert the MUFAs in liquid vegetable oils to TFAs (39). A recent study indicates that the effect of TFAs on the serum lipoprotein profile is harmful as it not only raises the LDL-C levels but also lowers HDL-C levels. The physical properties of TFAs are also very similar to SFAs (40). Thus care should be taken to avoid TFAs in diets as much as possible. Industry should be encouraged to point out on their labels the amount of TFA present in the hydrogenated oils and shortenings (40). Maximum safe allowable limits are still being considered but it would be advisable to keep the total TFA intake below 10 g/day.

Epidemiological and Intervention Studies

The earlier studies have conclusively proven that dietary modification can significantly reduce blood cholesterol which is the most important risk factor for the development of CHD (41,42). Most of these studies involve a reduction of SFAs and cholesterol and an increase in PUFAs or MUFAs. In most studies the morbidity from CHD declined significantly but the data were inconclusive as far as mortality was concerned (43-48). The large Multiple Risk Factor Intervention Trial (MRFIT) was designed to reduce the major risk factors in middle-aged men at high risk for CHD, high cholesterol, high blood pressure and excessive smoking. This study was carried out over a period of 6 years. The results indicated a significant reduction in risk factors in the intervention group with a minor reduction also in the control group (49). The linkage of high intake of PUFAs especially n-3 type from marine fish sources and a lower mortality from cardiovascular disease among Greenland Eskimos as compared with the neighbouring Danes was highlighted by pioneering studies by Dyerberg et al (50). The Eskimos were found to have significantly lower total cholesterol, LDL-C, VLDL-C and higher HDL-C than the Danish population. However, the major difference between the dietary fatty acid, n-3 and n-6, is the ability of the former to lower plasma triglycerides and VLDL in both normolipidemic and hyperlipidemic subjects. The reduction of VLDL levels by n-3 PUFAs is due to suppression of hepatic triglyceride and VLDL production. The n-3 PUFAs also induced a reduction of platelet aggregation by collagen and ADP, and also
prolonged the bleeding time in Greenland Eskimos as compared to an European control population. It is postulated that this was due to decreased arachidonic acid in the platelet phospholipids brought about by increased concentration of n-3 PUFAs. Similar studies with very encouraging results were published from Japan (51). Thus, dietary n-3 PUFAs from marine sources have an influence on atherosclerosis. However, on the basis of available data, no conclusions can be drawn on dose or composition of fish or fish-oil concentrates needed to optimise a potential antiatherosclerotic effect on humans (52,53). The Oslo Study Group primary prevention trial was carried out for 8.5 years and included 1,200 high risk cases. It demonstrated a reduction of CHD events including CHD deaths, sudden deaths, by about half, when the total fat intake was reduced from 41% in controls to 28% of energy, with an increase in the polyunsaturated/saturated fat (P/S) ratio from 0.4 to approximately 0.7 (54-56). These intervention studies have also demonstrated that by altering the P/S ratio to 0.7 there is a significant fall of cholesterol with a related overall reduction of CHD mortality by 50%. Results from the Seven Countries Study have shown that the Cretan diet combined a low intake of SFAs with a high intake of total fat to a liberal use of MUFAs in the form of olive oil. The American population is an example of high consumption of SFAs. The incidence of CHD in Cretan men was lower than would be expected from their total fat consumption and plasma cholesterol levels and could not be explained by other risk factors for CHD (57). Recently, the effects of natural diets containing 40 g/day olive oil or sunflower oil (62% linoleic acid) on serum lipoproteins and apolipoproteins in 20 healthy males and 11 healthy females living in closed religious communities were studied. Each dietary period was for 3 months and their life-style, physical exercise and body weight were kept constant throughout the study. Significantly higher DL-C and Apo A1 levels were seen during the olive oil period in both sexes when compared with the sunflower oil period. The atherogenic index (total cholesterol/HDL-C) remained unchanged in males, whereas in females a 21% increase in HDL-C was seen during the olive oil period which was responsible for a significant fall in the index during that period (36). Similar findings summarized by Grundy and Bonanome (58) have been reported by Baggio (37), Sirtory et al. (59) and Oya et al. (unpublished data) all suggesting a decline of LDL-C without affecting the HDL-C fraction after ingesting olive oil-rich diet. Also, olive oil in experimental studies has shown marked reduction of oxidized (denatured) LDL which is highly atherogenic. There was also reduction of end products of lipid peroxidation (58). The Edinburgh-Stockholm study was the first formal study demonstrating a
significantly lower proportion of adipose linoleic acid in a CHD. There was a significantly lower linoleic acid content in the adipose tissues of Edinburgh men compared with Stockholm men and on multivariate analysis, this turned out to be an independent risk factor (60,61). Similar results were shown by Oliver et al. (25) from North Karelia and Sapri (Calabria) (25). The recent European report of an inverse correlation between adipose linoleic acid and CHD showed an indirect evidence that increased consumption is beneficial. The Oslo heart study also produced similar results. In a comparative study of linoleic, alpha-linoleic and marine fatty acids, it was found that linoleic acid was far superior for lowering LDL-C (62). A recently work was carried out in normal subjects to study the effect of dietary n-6 fatty acids on the incorporation of dietary n-3 fatty acids in serum and thrombocyte phospholipids. The results showed that incorporation of n-3 fatty acids in phospholipids was reduced by a high intake of n-6 fatty acids in the cells and lipid fraction studied (63). The observed effect of dietary n-6 fatty acids was independent of the energy percentage provided by dietary fat. In order to obtain an optimal effect of n-3 supplementation, the intake of linoleic acid has to be considered and kept on a low level. The cholesterol content of serum was unaffected, but the concentration of triacylglycerol was reduced during the supplementation period (63).

Conclusions

The reduction of dietary cholesterol to below 300 mg/day produces a significant decline in the CHD risk for an individual. However, a more drastic restriction to approximately 200 mg/day total dietary cholesterol in moderate or high risk individuals can be extremely beneficial and may remarkably reduce CHD risk in these individuals. Reduction of all saturated fats to below the 10% level (of total energy intake) is a practical and useful goal. A further reduction to 6-8% level in well-motivated patients would be highly beneficial in moderate and high-risk individuals. MUFAs (mainly oleic acid) can be consumed easily up to 10-15% of total energy intake as a routine and liberally even up to 20% without significant concern provided the total energy intake is well within limits to maintain desirable weight for that individual. It is important to be aware of the TFA content in foods, oils and shortenings, but as yet no definite maximum limits have been set. n-6 PUFAs can be allowed up to about 7% of total energy intake. There should be more studies of populations consuming higher levels of n-6 PUFAs to determine whether increased intake improves health or not in long-term trials. n-3 PUFAs, on the other hand, can be increased to 2-3% or even more
with definite potential benefit. Eating fish and marine animals is the most documented and safe method for achieving this. However, larger intake particularly of fish oil supplements is still an unproven therapy for vascular disease and needs further substantiation to make it a regular mode of treatment for a variety of disorders. Increasing linoleic-acid intake is one of the things being studied extensively but still no consensus has been reached on the maximum daily allowance. There is a lot of evidence linking high dietary fiber with reduced CHD but results are still inconclusive, although suggestive. The soluble fibers are beneficial in doses of 10-20 g/day. In general, vegetarians have lower serum lipids and blood pressure than omnivores. Compared with high-fat mixed diets, vegetarian diet significantly lowers blood pressure, plasma cholesterol and LDL-C. Thus, recommendation of occasional vegetarian diets would be helpful to keep the lipids down. In high-risk cases a fully vegetarian diet may be extremely beneficial and may become one of the foremost modes of management in future. Thus the recommended strategies can be summarized broadly into three categories: (i) Reducing the flux of lipoproteins (reduce cholesterol absorption reduce total fat load and increase marine n-3 fatty acids). (ii) Enhanced receptor-mediated removal (reduce saturated fat intake, reduce cholesterol intake, and increase bile acid loss-fiber supplementation). (iii) Prevent modification of lipoproteins (increasing intake of antioxidants, especially vitamin E and A, and olive oil).

REFERENCES


