Lipids in the Prevention of Stroke

Gayle Crozier and Marco Turini

Nestlé Research Center, Lausanne, Switzerland

Stroke is defined as a clinical syndrome of neurological disabilities due to destruction of brain tissue caused by blockage of a cerebral artery. This blockage can be due to thrombosis or embolism, stenosis by atherosclerotic plaque, or to hemorrhage from a ruptured artery (1–4). It is the third most important cause of death after heart disease and cancer and is an important cause of long-term disability. The seriousness of a stroke depends on the location and extent of damage to the brain. Symptoms may be so minor that the victim is even unaware that one has occurred. On the other hand, major sensory loss, blindness, paralysis, speech loss, coma, and death can also be consequences. These effects, if they persist beyond a few weeks following the crisis, are likely to be permanent.

As indicated in its definition, stroke arises from two kinds of problems: those related to coagulation and those related to vessel integrity. The most common type in Western countries is thrombotic or embolic stroke, which accounts for around 80–85% and parallels the incidence of coronary heart disease. Hemorrhagic stroke, which accounts for around 15–20% of the total, reflects the frequency of hypertension. This chapter is mainly concerned with thrombotic stroke.

The etiology of thrombotic stroke is multifactorial but one of the main diet-influenced risk factors is existing coronary heart disease (5,6). There is evidence that dietary factors that contribute to this condition also increase the probability of cerebral accident. The relationship between dietary lipids and cardiovascular disease and thrombosis, as well as the potential of dietary lipids to prevent stroke, are reviewed in this chapter.

CARDIOVASCULAR DISEASE

Development of the Atherosclerotic Plaque

The circulation of blood in the vessel is responsible for normal wear and tear on the endothelial layer (Fig. 1); if these injuries are small and infrequent, they are reversible. However, where the circulation is particularly turbulent, continual injuries can lead to more serious damage, which eventually involves the underlying layers of the artery—the intima. Damage to the endothelial layer exposes collagen that
stimulates platelets to adhere to and aggregate at the surface of the injury. Growth factors released by the platelets influence smooth muscles to grow out from the media into the intima. The intima thickens due to a production of collagen from the smooth muscles. Continued deposition of platelets, fibrin, proteins, and blood lipids results in the formation of the fibrous plaque. These injuries can be exacerbated by the presence of free radicals, oxidized lipid particles, and certain nutritional deficiencies.

Macrophages arrive at the site to phagocytose the foreign particles including oxidized lipids. This lipid-laden macrophage is the origin of the foam cell—one of the earliest recognizable lesions characteristic of the atherosclerotic plaque.

**Thrombus Formation**

Damage to the vessel wall sets off the process of wound healing. Platelets are attracted to the site and aggregate together to form a platelet plug (Fig. 1). Damaged endothelium releases tissue factor that triggers the coagulation cascade. This results in the formation of a fibrin mesh which traps the clumps of platelets and red blood cells and seals the wound. This thrombus can become incorporated into the growing fibrous plaque. If occlusion of the artery is substantial, the thrombus can result in
complete infarction of the vessel and ischemia with resulting damage to the tissue irrigated by it. When this occurs in the heart, it is myocardial infarction; when it occurs in the brain, it is stroke.

Epidemiological studies have shown that many of the risk factors for cardiovascular disease are the same as those for stroke. Many lipid-related components of the diet have been implicated in the development of cardiovascular disease.

**LIPIDS AND CARDIOVASCULAR DISEASE**

**Cholesterol**

Serum cholesterol is a strong and consistent risk factor for coronary heart disease; however, for stroke it shows a J-shaped relationship. At low levels, risk of hemorrhagic stroke is increased, while at higher levels, risk of thromboembolic stroke is increased (7,8). Plasma cholesterol has been related to ischemic stroke to about the same degree as it has to coronary heart disease. This implies that diets that affect plasma cholesterol might also affect stroke (8).

This conclusion is somewhat controversial as two recent meta-analyses of cholesterol-reducing intervention trials in middle-aged men did not show any beneficial effect for stroke of lowering cholesterol (9,10). In these studies, as in any meta-analysis, no primary decision had been taken to examine the influence of cholesterol on stroke. No discrimination was made between thrombotic and hemorrhagic types of stroke and in all studies evaluated, only slight (7–15%) reductions in blood cholesterol were achieved.

Results of these studies were nonetheless compatible with a possible small effect—protective or harmful—that was not detectable. Dietary intervention appeared to be of greater (although not significant) benefit on mortality than clofibrate-induced cholesterol reduction (9).

**Dietary Fatty Acids**

There are five major groups of fatty acids: saturates, trans unsaturates, monounsaturates, n-6 polyunsaturates, and n-3 polyunsaturates. There has been a great deal of interest in their relative effects on blood lipids.

A typical fatty acid is characterized by a string of carbons that have a methyl group at one end and a carboxyl group at the other (Fig. 2). Saturated fatty acids are those fatty acids that do not contain a double bond, that is, they are completely "saturated" with hydrogen. An unsaturated fatty acid contains one or more double bonds. If it contains more than two double bonds, it is polyunsaturated. These molecules are identified by the nomenclature

\[ X:Y \ n-Z, \]

where \( X \) refers to the number of carbons in the chain, \( Y \) refers to the number of
Saturated Fatty Acids

Saturated fatty acids more consistently increase low-density lipoprotein (LDL) cholesterol than does dietary cholesterol itself. Common saturated fatty acids in the diet range from 8 to 18 carbons in length and not all have the same effects on blood cholesterol (Fig. 3) (11). Those 8 to 10 carbons in length—the medium chain fatty acids—do not raise LDL cholesterol but rather lower it.

The 18-carbon fatty acid, stearic acid, which is abundant in cocoa butter, does not raise cholesterol (12). The saturated fatty acids that are known to have a cholesterol-raising effect are lauric (12:0), myristic (14:0), and palmitic (16:0) acids, especially the latter two.

Current recommendations are to use saturated fat in the diet at less than 10% of total energy. Probably eliminating C12, C14, and C16 saturated fatty acids from the diet would have the most beneficial effect, but such a diet would be unpalatable, probably unacceptable, and thus such a recommendation would be ineffectual. Therefore, there is an opportunity for the food industry to manufacture foods that are low in the cholesterol-raising fatty acids by replacing them with other fats that do not raise cholesterol.

Trans Fatty Acids

Trans fatty acids exist naturally in fats from ruminant animals; about 4–8% of total fatty acids in butter are trans. Average consumption in the United Kingdom is
FIG. 3. The influence of dietary fatty acids on serum cholesterol: 1% dietary carbohydrate was substituted by 1% of the fatty acid in question (From ref. 11 with permission).

estimated to be 2% of total energy. When fed at high levels (10% of energy) (13), trans fatty acids raise LDL cholesterol almost as much as saturated fat. HDL cholesterol is decreased and serum triglycerides increased compared with oleic acid. When fed at lower levels, trans fatty acids still raise LDL cholesterol, although not as much as saturated fatty acids and do not change HDL (14). These studies raise the possibility that trans fatty acids contribute to atherogenesis by adversely affecting the LDL/HDL cholesterol ratio.

Monounsaturated Fatty Acids

The major monounsaturated fatty acid of the diet is oleic acid (18:1 n-9). It has no effect on blood cholesterol relative to carbohydrates. On the other hand, unlike oleic acid, carbohydrates have been shown to increase plasma triglycerides and lower HDL cholesterol and, in this sense, consuming oleic acid has advantages over consuming carbohydrate. The widely famed "Mediterranean diet" is rich in oleic acid because of its high content of olive oil, and rates of cardiovascular disease are low in the Mediterranean region. Whether this is an effect of olive oil, oleic acid, or other dietary or lifestyle factors is not certain.

n-6 Polyunsaturated Fatty Acids

Polyunsaturated fatty acids of the n-6 family are nutritionally essential and are very biologically active. The main n-6 fatty acids include linoleic acid (18:2 n-6),
\( \gamma \)-linolenic acid (18:3 n-6), and arachidonic acid (20:4 n-6). They enhance membrane fluidity, are precursors of eicosanoids, and have other specialized functions in the cell. In comparison to dietary saturated fatty acids, dietary n-6 fatty acids (mainly linoleic acid) lower LDL cholesterol. They have also been shown to decrease blood pressure, protect against cardiac arrhythmias, and slow the development of atherosclerosis. For these reasons, n-6 fatty acids have beneficial effects on cardiovascular health. However, because of their polyunsaturation, these fatty acids are susceptible to oxidation and there is accumulating evidence implicating products of peroxidation with the development of pathologies such as atherosclerosis and cancer. Studies of laboratory animals have indicated that high doses of linoleic acid can promote the development of cancer and depress the immune system.

Overall, these mixed properties give n-6 fatty acids the potential to be beneficial or detrimental to health, depending on the quantity consumed and the availability of other dietary components such as antioxidants. So far, the optimal level of linoleic acid in the diet remains controversial. Further knowledge of the balance of these positive and negative effects will allow us to make a more exact assessment of optimum linoleic acid intake. Present linoleic acid levels in the American diet are about 7% of total energy. The American Heart Association and the National Cholesterol Education Program both suggest maximum intakes of 10%.

\textit{n-3 Fatty Acids}

\textit{N-3 fatty acids}, like n-6 fatty acids, are nutritionally essential. The main dietary n-3 fatty acid is \( \alpha \)-linolenic acid (18:3 n-3) and two other important ones relevant to cardiovascular health are \textit{eicosapentaenoic acid} (EPA, 20:5 n-3) and \textit{docosahexaenoic acid} (DHA, 22:6 n-3). In the diet, these latter two fatty acids are derived primarily from fish. Small amounts of dietary fish oil increase the concentration of n-3 fatty acids in membrane phospholipids. This leads to changes in blood viscosity and membrane structure. The latter influences membrane fluidity and the activity of membrane-associated enzymes and receptors (15). The qualitative and quantitative synthesis of eicosanoid is also altered.

\textbf{Blood Lipids}

Many studies have shown that dietary fish oil has hypolipidemic effects without depressing HDL. In one well-controlled study (16), highly significant results were obtained in mildly hypertriglyceridemic men given fish or fish oil (4.5 g/d EPA + DHA). Plasma triglycerides and very low density lipoproteins (VLDL) were decreased and HDL cholesterol increased. Several studies have shown that there is less postprandial lipemia when the diet contains fish oil (17).
Thrombosis

Eicosanoids are products of the cyclooxygenase and lipoxygenase and are derived from 20-carbon fatty acids. They mediate many biological functions among which one is thrombosis.

Thromboxane $A_2$ (TxA$_2$), which is derived from arachidonic acid (20:4 n-6), has strongly proaggregatory effects on platelets and is a strong vasoconstrictor (Fig. 4). TxA$_3$, which is derived from eicosapentaenoic acid, has only weak aggregatory and vasoconstrictor effects. In vivo and ex vivo studies have shown that dietary n-3 fatty acids decrease the formation of TxA$_2$ and this is correlated with reduced platelet adhesiveness to collagen and fibrinogen (18), reduced platelet aggregation (19), increased platelet survival (20), and longer bleeding time (19).

Both arachidonic acid and EPA are precursors of prostacyclin, which is an antithrombotic and antivasospastic agent. The prostacyclin derived from EPA is thought to be as potent as, if not more potent than, that derived from arachidonic acid (21) and as easily synthesized. In a study of subjects scheduled for coronary bypass surgery, 4.3 g/d EPA + DHA fish oil increased prostacyclin production in the vascular tissue (22).

Some of the coagulation factors have been shown to be affected by dietary fish oil supplements. High plasma fibrinogen is one of the risk factors for cardiovascular disease. In one prospective study (23), men in the highest tertile of plasma fibrinogen had three times the risk of fatal or nonfatal heart attack. Plasma fibrinogen is affected by diet; it has been shown to decrease with high (6.4 g/d) (24) or low (2.2 g/d) (25) levels of fish oil supplementation. With 5.4 g/d EPA + DHA, plasminogen activator inhibitor-I decreased by 22% (26), whereas tissue plasminogen activator was not affected. These changes may help to explain the antithrombotic effect of fish oil.

![FIG. 4. Eicosanoids synthesized from arachidonic and eicosapentaenoic acids.](image-url)
Vascular Effects

In a study of subjects scheduled for coronary bypass surgery, 4.3 g/d EPA + DHA fish oil increased prostacyclin production in the vascular tissue (22). This increase in prostacyclin with fish oil feeding was associated with a significant decline in blood pressure in those subjects who initially had mild hypertension (21). No decline in blood pressure was noted in those who were normotensive to begin with.

Fish eating is associated with a decrease in atherosclerotic plaque formation. In a study of fishing versus farming villages, pulse wave velocity of the aorta was slower (indicating less atherosclerosis) in the inhabitants of the fishing village (27). The arterial wall characteristics of healthy fish-eaters were determined by Doppler ultrasonography to be better than in comparable control subjects (28). Advanced atherosclerosis at necropsy was found to be less in Alaskan Eskimos than in Alaskan non-natives (29).

There are several possible mechanisms to explain this. One is that platelet-derived growth factor has been shown to be diminished in the presence of fish oil in in vitro studies with endothelial cells (30). Fish oil also decreases the macrophage count and probably has suppressive effects on the immune reaction at the sites of vessel injury.

Population Studies

In the Diet And Reinfarction Trial (DART), 2,033 men under 70 years old were recruited during their recovery from myocardial infarction (31). Half the men were instructed to eat fatty fish at least twice per week whereas the others were not given this advice. Results after 2 years indicate that some protection is obtained from a modest intake of oily fish (about 300 g per week, corresponding to approximately 4 g n-3 fatty acids).

Two populations are known for their abundant consumption of fish—the Japanese and the Greenland Inuit. Both populations have high rates of cerebrovascular disease of the hemorrhagic type (32,33). In Japan, cerebrovascular disease was the leading cause of death in 1960. However, by 1985 it had fallen to third place (34). This fall was associated primarily with a substantial and significant fall in blood pressure. Over this time, salt intake had been reduced from 20 to 14.2 g per day and better compliance with taking antihypertensive medication was achieved.

Other Japanese dietary changes included doubling of animal fat intake and a reduction of fat consumed from fish. There has been a notable increase in mean blood cholesterol levels. There may also be a mild hypotensive effect of fish oil (35).

Fish consumption has been associated with a blood pressure lowering effect but this effect is mild and appears to be overridden by the effects of such high levels of salt. During the last 25 years, many other social factors such as better working conditions and better home heating have undoubtedly played a role in decreasing
blood pressure. In Japan, fish-eaters have fewer strokes. Studies of fishing versus farming villages have shown a higher fish consumption, higher n-3 fatty acids in the plasma, and significantly decreased mortality rates from cerebrovascular disease in the fishing village (36).

The relatively high incidence of hemorrhagic stroke among the Greenland Inuit (37) is not related to excessive blood pressure but has been associated with prolonged bleeding time and reduced platelet aggregation. These effects are consistent with the consumption of large amounts of sea food. Keli et al. (38) showed in a longitudinal study that Dutch men who suffered a stroke ate significantly less fish (12.8 g/day) than those who did not have a stroke (18.3 g/day). This study indicated that a regular moderate consumption of fish may be protective.

SUMMARY

Dietary lipids have many physiological effects that are related to the health and well-being of the vascular system. LDL cholesterol is a risk factor for thrombotic stroke and there is much evidence that LDL cholesterol is increased by the inclusion in the diet of saturated fatty acids of 12–16 carbons in length as well as by trans fatty acids compared to mono- or polyunsaturated fatty acids. On the other hand, consumption of monounsaturated fatty acids and reasonable levels of n-6 fatty acids, that is, linoleic acid, seems to have protective effects for the vascular system.

Many studies have suggested beneficial effects of the consumption of fish and fish oil in pathologies linked to excessive thrombosis and the formation of the atherosclerotic plaque. These conditions certainly include cardiovascular disease and stroke. Moderately increased consumption of fatty fish by individuals living in the Western developed countries could have beneficial effects for those at risk for cerebrovascular risk.

REFERENCES


DISCUSSION

Dr. Yamori: What is the mechanism of the decrease in fibrinogen?

Dr. Crozier: I don’t think it is known what the mechanism of the decrease in fibrinogen is. However, the nutritionally essential fatty acids have many effects at molecular levels and are known to regulate at the gene level. It wouldn’t surprise me if this were the way that the fibrinogen decreases occur—through gene regulation.

Dr. Yamori: What do you think of the effect of cholesterol on stroke? We observed initially that, in Japan, the serum cholesterol level tended to be low and a moderate increase in serum cholesterol level actually prevented stroke.

Dr. Crozier: Japan is a very special place because most of the strokes are of the hemorrhagic type related to the very frequent occurrence of hypertension. That is quite a different situation than the thrombotic stroke. The work that I have seen relating serum cholesterol to hemorrhagic stroke incidence shows that there is absolutely no correlation or, if there is, it is negative, that is, that the lower the cholesterol, the more hemorrhagic stroke there is. However, with respect to thrombotic stroke, the more cholesterol, the higher the incidence of thrombotic-type strokes.

Dr. Yamori: In Japan, thrombotic stroke is also increasing. It has two causes, atherothrombotic stroke and atheronecrothrombotic stroke. The pathogenesis of these two types of stroke is quite different. Cholesterol is only involved in the pathogenesis of atherothrombotic stroke; it may even have a preventive effect in atheronecrothrombotic stroke. We have already reported that cholesterol metabolites decrease blood pressure, so it appears that cholesterol may even be doing some good!

Dr. Crozier: It is very important to stress that any nutrition advice must be taken in the correct context. For example, it is probably a good thing to decrease serum cholesterol in atherosclerotic thrombotic stroke, but in other kinds of stroke, it may not be at all appropriate, for instance in the hypertensive hemorrhagic type of stroke.

Dr. Guesry: I think we should not be tempted to claim that Japan is special and does not fit with the theory. On the contrary, I think it fits very well. There is currently a change in both diet and stroke epidemiology in Japan, but the Japanese diet on the whole explains very well why there is less thrombotic stroke and more hemorrhagic stroke.

Dr. Hennerici: You have addressed the subject of a special diet for cholesterol regulation. You have not addressed the enzymatic process that regulates the cholesterol level in the blood with respect to storage. We all know there are studies in which there are individuals who have a very effective enzymatic system, who can eat whatever they want and still have low cholesterol values; they have all the risk factors which you indicated but they are quite normal. So what do we know about this relation between intake and diet on the one hand and the inborn systems of enzymatic control which prevent atherosclerotic disease if they are functioning reasonably well?

Dr. Crozier: I think the most important thing is for us all to have parents who live to be 100 years old. Genetics plays an extremely important role in all this, far stronger than nutrition in my opinion. If we are born with those enzymes or enzyme activities in genes which are protective, then we can live to be 100 years old. However, I think that until we have information...
to the contrary, it is probably wise to live prudently and to eat diets which are known to have beneficial health effects.

Dr. Elmadfa: You advised us to increase the consumption of n-3 fatty acids but we still do not have any recommendations about the ratio of n-3 fatty acids to total polyunsaturated fatty acids. Have you got any new information on this?

Dr. Crozier: n-3 has been going down. There are estimates that, at present, we eat a ratio of n-6 to n-3 of around 50 to 1 or 20 to 1, and we should be eating about 10 to 1, so we should either decrease our n-6 or increase our n-3; probably both strategies would be appropriate.

Dr. Elmadfa: This ratio you mention is estimated in milk fat, but in a mixed diet, we have a ratio of about 6 to 1 n-6 to n-3 fatty acids.

Dr. Crozier: I would like to see where that information comes from. I dispute it. The information I have seen has shown the ratio to be a lot higher than 6 to 1.

Dr. Zurloh: I think there is evidence that the n-3 fatty acids, in particular, docosahexaenoic acid (DHA), are present in greater amounts in brain tissue than in other tissues. Do you think there is a correlation between stroke and the content of n-3 fatty acids in the brain tissue?

Dr. Crozier: Eicosapentaenoic acid (EPA) is the one which exerts effects on the platelets. DHA is the richest n-3 fatty acid in the brain by far, but I don’t think that its main business is to handle thrombosis. DHA has six double bonds and, as I mentioned, fatty acid will bend with each double bond and so DHA is thought to have a helical structure. This is a fatty acid that plugs itself into the membrane and serves as a channel for ions and other signals which are coming through the membrane. I have the feeling that that is the most important function of DHA in brain.

Dr. Zurloh: But do you think there is any correlation between the prevention of stroke and the composition of brain tissue itself?

Dr. Crozier: Because it has so many double bonds, DHA is highly oxidizable. Thus, if you have a hemorrhagic type of stroke which releases a lot of iron into the brain, the presence of oxidized lipids may perhaps be beneficial in that situation by acting as antioxidants. It is normal for brain to be very rich in DHA. Children who are born with peroxisomal deficiencies, for example, are unable to make DHA and those children have failure to thrive and serious mental retardation, so DHA plays a very important fundamental role.