REVIEW

The role of eggs, margarines and fish oils in the nutritional management of coronary artery disease and strokes

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Abstract. Although egg yolk is a rich source of cholesterol, the effect of eggs in raising serum cholesterol is variable and in some subjects there is no effect whatsoever. However, oxidized cholesterol can increase atherosclerosis even with normal serum cholesterol. In order to attenuate oxidation of cholesterol in eggs, it is necessary to limit the degree of heat applied. This means that we should use only soft-boiled eggs which should be almost like water. We can also avoid egg yolk altogether and get a highly nutritious egg food from the egg white alone. The saturated fats from milk products, especially butter, are highly atherogenic. There are available many butter substitutes in the form of margarines. But many of these margarines have hydrogenated vegetable oils which result in the production of trans-fatty acids. The trams-fatty acids are as atherogenic as saturated fats. There are available, however, margarines without the trans-fatty acids. These are found only in large supermarkets. Fish oils contain N_3 fatty-acids which, unlike vegetable oils which contain N_6 fatty-acids, can prevent atherosclerosis and sudden death by counteracting ventricular arrhythmias, acting as antioxidants, antithrombotic, anti-inflammatory agents, and decreasing triglycerides and blood pressure. (Keio J Med 53 (3): 131–136, September 2004)

Key words: cholesterol, eggs, fish oil, margarine, trans-fatty acids

The Nutritional Management of Coronary Artery Disease and Strokes

How to minimize the dangers of egg cholesterol: the egg story

In 1912 Anitchkow in Germany fed egg yolk cholesterol to rabbits and produced aortic atherosclerosis.[1] This was the first widely publicized proof that there was a connection between atheromas and cholesterol. The word ''atheroma'' comes from the Greek ''athero'' which means porridge or gruel plus ''oma'' which means tumor. This is the fatty cholesterol-rich lump found in the lining of the blood vessels. When calcium is added to the lump it is called ''plaque'' and the condition is called ''atherosclerosis'' (sclerosis is Greek for ''hard''). When the lining of the plaque or atheroma ruptures, the fats burst through into the lumen. These fats are very thrombogenic and the clot can cause a complete obstruction known in lay term as ''heart attack'' but in medical terms as a ''myocardial infarction.''

About 65 years after Anitchkow's experiments, three American groups fed purified cholesterol to rabbits and could produce no atheroma.[2–4] When Anitschknow's methods were analyzed, it was apparent that his egg yolk cholesterol had had ample time to be exposed to air which allowed the cholesterol to be oxidized. Oxidized cholesterol when fed to rabbits produces angiotoxic effects in the coronary arteries within 24 hours and ultimately results in atheromas.

In 1904, Schutze had described the oxidation of cholesterol by air.[5] Improperly stored cholesterol in air contains at least 32 auto-oxidization products, some of which have lethal toxic effects on the arterial walls that can lead to atheroma.[4] Atheromas removed from human aortas contain these oxidization products.

Half of the cholesterol in the blood is due to diet and half comes from the liver and other tissues. The endogenous cholesterol produced by the liver and other tissues does not cause atheromas because endogenously produced cholesterol is probably protected from auto-

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oxidation by antioxidants present in most animal organisms.[2,6]

Because egg yolk is a major source of cholesterol, it is natural to assume that we should avoid eggs as much as possible in order to lower our serum cholesterol. The assumption that eggs should raise serum cholesterol was first tested in 1960. On the usual high saturated fat Western diet, it was found that six to twelve weeks of two to fourteen eggs/day had no effect on cholesterol.[7,8] However, on a low saturated fat diet, Connor found that although he could raise the cholesterol with six to eight eggs/day, to his surprise, six eggs/day produced no greater increase in serum cholesterol than two yolks. This suggests that the G.I., tract has a limited capacity for cholesterol absorption. Another surprise was that when taken with polyunsaturated fats (mostly vegetable oils) the cholesterol rose higher than without those polyunsaturated fats.[9,10]

The studies on the effect of egg intake on serum cholesterol is confounded by the presence of hyperresponders and hypoerresponders to cholesterol intake, an inheritable condition. They may account for the finding by Kummerow, *et al.*[11] that two eggs/day in three different countries resulted in an increase in cholesterol in some and a decrease in others. Usually when a study was carried on over a period of at least eight weeks there was no difference in cholesterol levels. When a reduced fat diet was used together with two to seven egg/week, hyperresponders to cholesterol showed no effect at eight weeks, *i.e.*, the hyperresponse effect is only temporary.[12]

The above research suggests that we should not be concerned with the amount of cholesterol ingested in high cholesterol foods but we should be more concerned with whether or not the cholesterol is oxidized, especially now that it is widely known that oxidized LDL is the culprit in causing atherosclerosis. Oxidized cholesterol can not only result in ulceration and rupture of plaques which can lead to thrombosis[13] but some oxidized cholesterol products have also been found to be carcinogenic.[14,15]

Aside from autooxidization in air, the most powerful method of oxidizing cholesterol is by heat. Heated egg yolk and milk can produce atheromas in hamsters, an animal known to be resistant to atherosclerosis.[16] Today's egg industry puts out eggs free of oxidation products. In rabbit feeding, fried or hard-boiled eggs produced the highest serum cholesterol (10 to 14 times the experimental level). Scrambled eggs increase cholesterol six to seven times above the preexperimental level, and soft boiled eggs increase it by only three to four times.[4] Other high cholesterol foods such as milk fat become oxidized during the pasteurization process. Powdered milk is exceptionally high in oxidization products. Cheeses exposed to air for long periods during processing and stored at room temperature are likely to contain significant toxic cholesterol oxidation products.

Thus, if we wish to minimize the ingestion of oxidized cholesterol, we should prepare our eggs to be soft boiled or soft fried (''sunny side up''). These eggs still have small amounts of oxidized cholesterol and they are therefore a compromise. Our milk products should be either non-fat or contain 1% fat. For those whose fear of the small amount of cholesterol in a minimally heated egg yolk is too strong for comfort, there are available whole egg substitutes. The egg yolk is removed and the egg white is sold with yellow color added in the form of beta-carotine which our bodies turn into vitamin A. These are available in all supermarkets and in many American restaurants, the most popular being ''Eggbeaters.'' Egg whites are a high protein food that contains all the vitamins and minerals of the whole egg. One-quarter cup contains even a greater vitamin A, thiamine, riboflavin, vitamin E, B6, and B12 content than the whole egg. They may also be preferred by the calorie conscious person because they have only about one-third the calories of the whole egg.

Butter substitutes: the margarine story

It is well known that saturated fats (all anima-derived fats) are the strongest method of raising serum cholesterol. In order to avoid butter which is very high in saturated fat we naturally turn to margarines which are made of vegetable oils which have no significant amounts of saturated fat or cholesterol. The problem with margarines is that the wrong ones can have the same effect as saturated fat, depending on how hard they are. In order to make the vegetable oils hard enough to spread on bread, hydrogen must be added. The more hydrogenation, the more saturated and the more atherogenic they are. The stick margarines are the hardest. Therefore, soft tub margarines are preferable. If the first ingredient on the label is the oil, then it has the least hydrogenation.

Unfortunately, the more hydrogenation, the more it produces atherogenic fatty acids called transfatty acids.[16] They may be worse than saturated fats in that they not only equal saturated fats in increasing the bad cholesterol known as LDL, but also decrease the good cholesterol known as HDL. Saturated fats do not lower HDL.[17] It is helpful for the memory to think of the first ''ll'' in LDL as ''lethal'' and to think of the first letter in HDL as ''healthy.'' The soft tub margarines have about one-third of the amount of the amount of transfatty acids as the hard stick margarines. To make matters worse, transfats are not usually listed as saturated fats on product labels, although new legislation is promising to change that. Replacing butter by soft margarines was

found to favorably affect blood lipids, and may reduce the risk of coronary artery disease, but hard margarines conferred no benefit whatsoever over butter.[16] Merely switching from butter to margarine without regard to the degree of hydrogenation is counterproductive as suggested by the finding that in 1950 Norway launched a cholesterol-lowering campaign in which soy margarine replaced butter. In the next 20 Years, there was a steep rise in deaths from coronary thrombosis.[18]

There are now available margarines that have no transfatty acids. Some also have added stanol esters which are products of vegetable oils that can actually lower serum cholesterol. The trade names in the USA are Benecol, Smart Balance Plus, and Take Control. In almost every supermarket in Europe or North America you can find margarine that has no transfatty acids. Those that have stanol esters added are probably preferable.

ω-3 (N_3) Fatty Acids: the Fish Story

Epidemiologic studies

Greenland Eskimos rarely have coronary artery disease despite their high fat diet. They were found to have low cholesterol, low triglycerides, and high HDLs. Eskimos who repatriated to Dermark lost their beneficial lipid profile. The diet of the Greenland Eskimos is low in saturated fat and high in a kind of polyunsaturated fat known as ω-3 or N_3 fatty acids. This is in contrast to the N_6 fatty acids which are preponderant in vegetable oils that contain linoleic acid such as corn, soy and safflower oil.

Mortality from coronary artery disease and stroke in a Japanese fishing village where fish supplied a high amount N_3 fatty acids was much lower than in a nearby farming village where the consumption was only less than one-half of the farming village N_3 fatty acids per day. In the Netherlands a 20-year study showed that two fish dishes (even flounder or cod) a week resulted in a 50% less likelihood of dying from coronary disease than those who ate no fish.[19] This is surprising because flounder and cod have the lowest percent of N_3 fatty acids of all the fish. The fattier the fish, the more N_3 fatty acids are present. The fatty fishes are those from cold ocean water; the highest being Norwegian sardines, Chinook salmon and Atlantic mackerel. The lowest is haddock which has about one-fifth of the N_3 that is in salmon. Tuna has one-half of that in salmon. This suggests that the Netherland study was successful not because of the fish intake per se, but probably because at least two meals a week were devoid of meat and its saturated fat.

Three other studies: one Swedish (14 Years) and two USA (20 years and 25 years) showed an inverse relation between fish consumption and the risk of coronary artery disease.[20]

The N_3 fatty acids and sudden cardiac death

One study found that coronary occlusion and ventricular fibrillation that occurs during reperfusion can be prevented in animals by feeding them tuna fish oil.[21] Patients with heart disease who had the highest levels of N_3 fatty acids had the lowest incidence of myocardial infarctions and sudden death.[22] In one study if they ate fatty fish only once a week, there was a 50% decrease in primary cardiac arrest. However, this did not include fried fish or fish sandwiches.[23,24]

Fish oil

The commonest fish oils used in research contained two N3 fatty acids, eicosapentanoic (EPA) and docosahexanoic acid (DHA). The commerical capsules used have usually been either Max EPA or Promega which have both EPA and DHA fatty acids. Humans can manufacture N_3 fatty acids from linolenic acid which is found in some vegetable oils. There may be enough linolenic acid in a normal Western diet to equal one to two fish oil capsules per day.[25] The liver can adjust the conversion rate to equal what the body needs, thus we can prevent overdosing with fish oils.

N_3 fatty acids as antioxidants

Fish oil can decrease the oxidation products generated by the inflammatory cells which accompany ischemic reperfusion. But fish oils themselves may be oxidized. Antioxidants such as vitamin E and vitamin C can prevent fish oil oxidation. Fish oil feeding is a classical method of producing vitamin E deficiency in animals.[26] Cod liver oil capsules usually come with a suboptimal amount of vitamin E added as an antioxidant.[27] When concentrated N_3 such as Max EPA is fed to animals no peroxides are produced, and so no antioxidants are necessary.

N3 effect on platelets, thrombosis, and bleeding

Thromboxane from platelets causes vasconstriction, platelet aggregation and thrombosis. Prostacycline is derived from vascular endothelial cells and causes vasodilation and decreases platelet aggregation. N3 fatty acids decrease thrombosis by decreasing the output of thromboxane from platelets and increasing prostacycline and fibrinolysis.[28,29] Although only large doses of fish oils can decrease fibrinogen levels and increase fibrinolysis,[30] even moderate doses of cod liver oil can

increase bleeding time.[31] Long term fish oil feeding or a high intake of fish can increase bleeding time by producing platelet changes. These changes in Greenland Eskimos are so marked that they bruise easily, have profuse nosebleeds and cerebral hemorrhages. They usually often die of internal hemorrhage from moderate injuries after falling into a hole in the ice.[22,27] However, there have been no reports of bleeding or increased cerebral vascular hemorrhage in Japan fishing villages or in clinical trials with fish oil supplements.[27]

The inhabitants of a fishing village in Japan showed a lower blood viscosity.[32] Many studies have shown that fish oil supplements can decrease whole blood but not plasma viscosity suggesting that the N_3 fatty acids make the red blood cells more deformable. This would help attenuate ischemia.[32–34]

One study suggested that the decrease in thrombosis by N_3 fatty acids is not due to a fall in thromboxane decreased platelet aggregability[35] but probably due to the effect of N_3 on tPA. tPA is a tissue plasminogen activator, the inhibition of which would cause thrombosis. N_3 can block the inhibition of tPA.[36] N_3 in large doses can also cause a fall in antithrombin III.[37]

Selenium supplements have been known to prolong bleeding time and low selenium levels are associated with an increased risk of coronary artery disease.[38] Fish contains selenium which is rare in other foods.

Fish oil and atherosclerosis

In The Greenland Eskimos myocardial infarction was one-tenth that of the nearby Danes. In patients with coronary artery disease those with higher levels of N_3 had fewer myocardial infarctions and sudden death.[22] A fishing village in Japan had a lower incidence of myocardial infarction and strokes than the nearby dairy farming village who also had one-third of fish had the N_3.[34]

Those Swedes who eat little or no higher incidence of myocardial infarction and angina than those who ate much fish.[40] Fish oil fed to rabbits and two species of monkeys all of whom were placed on atherogenic diets decreased the degree of aortic atheromas and had smaller induced infarction size.[39,40]

Fish oils, cholesterol, trigicerides and HDL

Moderately high fish diet, *i.e.*, fatty fish twice a week, produced a non-significant effect on cholesterol, LDL and HDL. However, the triglycerides do decrease significantly.[41–43] Although fish oil does not increase cholesterol much, it does prevent it from rising if the patient has a very high cholesterol intake.[44,45] In most studies where fish oil did decrease LDL or cholesterol, the patients were also on a low saturated fat diet.[6] Some fish oil capsules can actually increase cholesterol and LDL because they contain relatively large amounts of cholesterol and saturated fats. Other capsules which contain no cholesterol and only a small amount of saturated fats may decrease LDL. Therefore you must look at the ingredients to know the effect of fish oils on lipids.[41,46] In studies using very fatty fish such as mackerel and sardines for as little as two weeks, there is a depression of triglycerides and an elevation of HDL. The conclusion must be that fish oil capsules can only be recommended for severe hypertriglyceridemia with a danger of pancreatitis. Otherwise, only increasing fish intake is recommended.[47]

N3 fatty acids' inflammation, allergy and vasospasm

Interleukin 1, tumor necrosis factor, and leukotriene 4 are stimulated by inflammation. All three are inhibited by N3 fatty acids.[22] N3 fatty acids also increase the responsiveness of T lymphocytes to inflammation and decrease their adherence to neutrophils. Some of the advantages to the above are that they may decrease the inflammatory response to rheumatoid arthritis,[48] and may benefit patients with psoriasis and atopic dermatitis.[49] The nephrotoxicity of cyclosporine decreased with fish oils.[50]

Primary Raynaud's symptoms completely resolved in 50% of patients over 12 weeks of fish oil ingestion. The other 50% could keep their hands in cold water 50% longer. Secondary Raynaud patients received no help from fish oils.[51] Fish oils are also effective for refractory migraine.[52] However, cardiac allographs in rabbits given fish oil develop accelerated coronary atherosclerosis.[53]

Fish and fish oils on blood pressure

A daily intake of fatty fish, *i.e.*, mackerel, for two weeks can diminish systolic pressure by about 10 mmHg.[54] However, fish oil had more questionable effects in other studies. In one study fish oil supplements had no effect on blood pressure[55] while in another study large doses of Max EPA lowered the blood pressure.[34] In diabetic patients on hemodialysis low dose fish oils can lower systolic blood pressure by about 10 mmHg.[56–58] Cod liver oil may be more specific for blood pressure because even one or two capsules daily (which will yield about 100 international units of vitamin D) can produce a modest fall in blood pressure.[31]

In vegetable oils the N3 polyunsaturated fats are of three types: 1. Twelve carbon chains as in alpha linolenic acid, 2. Twenty carbon chains as in EPA, 3. Twenty-two carbon chains as in DHA. The alpha linolenic acid comes from plant oils, especially canola, flaxseed, soy bean, walnut and evening primrose oil.

Humans can convert a portion of alpha linolenic acid to EPA and DHA.[59] If enough alpha linolenic acid is consumed, the body will form enough EPA and DHA without the need for fish oils.[60] Even in the normal diet humans can get enough linolenic acid to produce enough N3 to equal one to two fish oil capsules daily.[25]

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