

Fish or Fish Oil in the Diet and Heart Attacks

MAURICE E. STANSBY

Introduction

Research has shown that polyunsaturates in the human diet reduce serum cholesterol levels and probably thereby reduce risk of heart attacks, whereas saturated fatty acids exert the opposite effect. Fish contain certain polyunsaturates but also often equivalent amounts of saturates. Vegetable oils, on the other hand, contain principally polyunsaturates.

Nevertheless, fish oils reduce serum cholesterol levels to a greater extent than do vegetable oils (Peifer et al., 1960). While work on effect of polyunsaturates of fish oil on serum cholesterol levels was being done, a 20-year clinical study (Nelson, 1972) indicated that fish oils were much more effective in reducing incidence of fatal heart attacks in heart patients than were any other polyunsaturated oils. The reasons for these differences, which seemed quite illogical, were then unknown.

ABSTRACT—Recent research has shown that fish oil (or oil in fish), in addition to its role as a serum cholesterol depressant, also contains long-chain omega-3 fatty acids which may directly lower the risk of heart attacks. The only dietary source of these omega-3 fatty acids are fish flesh or fish oil. They can, at present, best be obtained by increasing consumption of fish in the diet. Efforts are underway to find an inexpensive way of producing fish oil concentrates for taking in capsule form. Until this happens, the best way to increase the omega-3 fatty acids in the human diet is to increase the consumption of fish.

Recent Research Findings

Current research, some of which began a little over a decade ago, is revealing the reasons for the superior effectiveness of fish oils. Much of this research prior to 1981 has been summarized in the last three chapters of a recent book (Barlow and Stansby, 1982). This research has shown that the omega-3 long-chain fatty acids found in food to any considerable extent only in oils of marine origin can act to reduce blood platelet aggregation and thereby reduce the risk of heart attack. This effect is quite separate and in addition to the well known reduction of serum cholesterol levels by polyunsaturates.

Research was begun in the early 1970's to determine why Eskimos in remote areas of Greenland almost never suffered heart attacks. It was found that the protection against heart attacks was associated with the Eskimo diet which consisted almost entirely of the flesh of marine fish or marine animals. Further research related the effect to the presence of eicosapentaenoic acid and possibly other long-chain omega-3 fatty acids derived from the Eskimo's marine food (Dyerberg, 1982).

Most of the original work by Dyerberg and his co-workers (Dyerberg, 1982) focused on the omega-3 fatty acid, eicosapentaenoic acid, as the fish oil

Maurice E. Stansby is a Scientific Consultant with the Northwest and Alaska Fisheries Center, National Marine Fisheries Service, NOAA, 2725 Montlake Boulevard East, Seattle, WA 98112.

fatty acid involved in decreased platelet aggregation. For some time it was assumed by many researchers that only the eicosapentaenoic acid was effective in this role.

This idea perhaps originated from the analogy that eicosapentaenoic acid very closely resembles the chemical structure of arachidonic acid, the former having merely an additional double bond in the omega-3 position. In the normal diet, arachidonic acid is the fatty acid which acts as the precursor for prostaglandin formation. Thus the theory probably developed from assuming that the eicosapentaenoic acid, replacing the very similarly structured arachidonic acid, was required to bring about the metabolism involving omega-3 structured fish oil fatty acids to prostaglandins which could then diminish thrombotic events.

At a London symposium on nutritional evaluation of long-chain fatty acids of fish oils in October 1981, a portion of the papers and the subsequent discussion dealt with the role of fish oils in alleviating heart disease and other conditions. During the discussion following the paper presentations, the matter of whether only eicosapentaenoic acid was required or if other omega-3 fatty acids were involved was considered in some depth (Barlow and Stansby, 1982:307-311). Partly based upon his earlier work (Lands et al., 1973), W. E. M. Lands concluded that the diminishment of thrombotic events was caused by activity of any long-chain omega-3 fatty acid to inhibit prostaglandin biosynthesis. Even J. Dyerberg, al-

though indicating that most of his research dealt with eicosapentaenoic acid, also felt that other long-chain omega-3 fatty acids could be involved.

Today, the opinion seems to be gaining favor that any long-chain omega-3 fatty acids may be involved. In fact, there is some belief that the more highly polyunsaturated fatty acids such as docosahexaenoic acid may be even more effective in this regard than eicosapentaenoic acid. Manufacturers of long-chain fish oil polyunsaturated concentrates for dietary use are now emphasizing production of mixtures of omega-3 fatty acids or of increasing the content in such concentrates of the docosahexaenoic acid.

Since the first publications in Denmark presenting ideas on the reasons for virtual immunity of Greenland Eskimos to heart attacks, well over 100 scientific papers have confirmed and extended these results. These studies have been underway in many different laboratories throughout the world. In addition to the work on the mechanism for the action of omega-3 fatty acids from fish oil influencing through prostaglandins formation formed in such a way as to decrease platelet aggregation and thereby to reduce incidence of heart attacks, many papers have shown a similar mechanism for the action of anti-inflammatory drugs such as aspirin on heart attacks. Three European scientists won in 1982 the Nobel prize in medicine for this work. One of these three (John Vane) had authored with Dyerberg a paper (Dyerberg et al., 1978) on this effect when fish oil was involved.

In addition to this effect on heart attacks, apparently with some animals by a similar mechanism, omega-3 fish oil fatty acids can affect the severity of the after-effects of strokes. In experiments with cats, Lands (1982) showed that those animals fed omega-3 fatty acids from fish oils showed a decrease in the extent of such effects.

Serum Cholesterol vs. Omega-3 Effects

Much of the early work on serum cholesterol depressant activity of fish oil (summarized by Stansby, 1969) showed merely that fish oil was at least as effec-

tive, usually more so, as other polyunsaturated oils in lowering serum cholesterol levels. In most cases where population groups (e.g. Japanese fishermen's families with high fish consumption rates) had diminished thrombotic events, it was assumed that the effects upon decreased heart attacks were due solely to reduction in serum cholesterol levels. Recent research on families of Japanese fishermen (Hirai et al., 1980; Kobayashi et al., 1981) confirms that at least a part of the effect stems from intake of eicosapentaenoic acid.

In the 20-year study of Nelson (1972), the use of increased fish in the diet resulted in decrease of subsequent fatal heart attacks to less than one-fourth of that of the controls. In the absence of any other causes known at that time, the results were laid to lowering of serum cholesterol levels. At this late date, there is no way to discriminate as to cause. However, since the reduction in fatal heart attack was far greater than in any other known clinical experiment, it now seems highly probable that the newer discovered omega-3 mechanism was partly involved.

Very recent research has been concerned to a large extent with determining more precisely the mode whereby the ingestion of omega-3 fatty acids bring about decreased platelet aggregation. The question as to whether the effect is due primarily to eicosapentaenoic acid or to other long-chain fish oil omega-3 fatty acids as well is a difficult one to answer. The two most commonly occurring such acids in fish oils are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). In oils from some species EPA occurs to the greatest extent; in others DHA predominates. There is always, however, more by far of either of these two omega-3 fatty acids than any others. It is very difficult and expensive to separate DHA from EPA. While for gas chromatography standards of pure DHA or EPA is available, the cost is so great (around \$100/g) that it makes use of these pure long-chain omega-3 fatty acids prohibitively expensive for research on their respective mode of action. In such work, it is common to use either fish oils or manufactured concen-

trates of EPA and DHA. Such research does not permit discriminating as to the effectiveness of either since both occur often at about equal concentrations.

While many current investigators are assuming that the main effect of the omega-3 fatty acid is a matter of incorporation of the omega-3 characteristics into the prostaglandin, it must be remembered that there is an entirely different mode of action which may be important involving inhibition of production of prostaglandins. Lands et al. (1973), showed that polyunsaturated omega-3 long-chain fatty acid inhibited prostaglandin synthesis, and the greater the degree of polyunsaturation, the greater was this inhibition effect.

Most of the very recent research has employed in vitro experiments on the role of EPA or a mixture of EPA with other omega-3 fatty acids on aggregation of platelets, but Fisher and Weber (1984) have shown, using in vivo techniques applied to human subjects, that mackerel oil high in EPA forms prostaglandin I₃.

In other recent work the commercially sold concentrate of EPA and DHA, Maxepa¹, which contains roughly equivalent amounts of EPA and DHA, has been investigated for its effect on platelet function in human patients (Sanders and Roshanai, 1983; Saynor et al., 1984). In both studies, positive effects were obtained upon the platelet function. It is interesting to note, however, that in the work of one laboratory (Saynor et al., 1982) the entire effect was laid to the EPA present and it was not even mentioned that DHA was present in the Maxepa used in the experiment. On the other hand, in a paper from a different laboratory using the same Maxepa product (Sanders et al., 1983), credit for the effects was attributed to both EPA and DHA.

Dietary Consumption of Omega-3 Fatty Acids in Fish Oil Concentrates

Dietary omega-3 fatty acids can be

¹Mention of trade names or commercial firms does not imply endorsement by the National Marine Fisheries Service, NOAA.

increased either by consumption of concentrates of fish oil in capsules or by increasing the amount of fish in the diet. At present there is one such encapsulated fish oil product available for sale in the United States. However, it is so expensive that it would cost about \$600/month for an individual to attain the same dietary level of omega-3 fatty acids as did the Greenland Eskimos who rarely suffered heart attacks.

Cheaper ways of concentrating omega-3 fatty acids in fish oils are being studied. Initially fish oil concentrate manufacturers believed that the single omega-3 fatty acid with chain length of 20 carbon atoms and five double bonds (EPA) was the only effective one for reducing heart attacks. However, it remains difficult and expensive to isolate a single fatty acid.

Now, however, with the likelihood that any long-chain omega-3 fatty acid will be at least as effective as EPA in bringing about the desired effect, efforts are underway in several countries, especially in Japan, to develop a better and cheaper method of concentrating the omega-3 fatty acids. Meanwhile, the most practical way to obtain omega-3 long-chain fatty acids is to eat more fish.

Omega-3 Fatty Acids From Fish in the Diet

Consumers who wish to improve their dietary levels of long-chain omega-3 fatty acids should select fish of relatively high oil content. The oil content of fish flesh may vary by more than 200 times (from 0.1 to 20 percent or more). This is not just a matter of variation from species to species. The oil content in flesh even of the same species may vary by more than ten times depending upon the area and season in which the fish is harvested. The oil content is controlled by the particular feed available to the fish.

The content of long-chain omega-3 fatty acids in fish of different species also varies to some extent but this variation is much less important in selection of fish for their omega-3 content than is the fat or oil content. While the content of any one long-chain omega-3 fatty acid may vary considerably in oils from different

fish species, the sum total of all long-chain omega-3 fatty acids has a much smaller variation.

Ways to select fish of high oil content based upon such factors as choosing cuts of fish from near the head where the oil content is greatest have been discussed in an earlier paper by Stansby (1973).

Greater consumption of fish generally considered to have high or medium oil content (Stansby, 1962) would be most desirable. These are species of fish in which the oil content, while varying considerably, is nearly always at least 5 percent. Examples include herring, mackerel, rainbow trout, all species of salmon (except chum), sardines, and albacore (if caught near California).

Low oil content fish vary in oil content from 0.1 to 5 percent. Those species in the upper range of this category (2 to 5 percent) furnish enough omega-3 long-chain fatty acids to be useful as a limited supply of such acids. Fish in this category include most tunas, carp, chum salmon, mullet, swordfish, and Great Lakes white fish. For shellfish such as oysters and clams, although the oil content usually does not exceed 1 percent, the oil is considerably higher in the omega-3 long-chain fatty acids. Such shellfish, therefore, can be included in this category despite their lower oil content.

Most of the species of fish listed here are available in the fresh state for only a part of the year. An exception are fish like rainbow trout which are grown by aquaculture and are available year-round. Rainbow trout also is one of the species with the highest total omega-3 long-chain fatty acids content. Canned albacore (which can be identified by the label "white meat" tuna) can contain considerable amounts of omega-3 long-chain fatty acids if the fish have been caught close to California. Other canned albacore and other canned tunas have a lower oil content and hence less of the omega-3 fatty acids.

Level of Omega-3 Fatty Acids Needed to Insure Some Significant Diminishment in Heart Attacks

It is much too early to reach any con-

clusion as to the minimum amount of fish or omega-3 fatty acids in the diet which is required to significantly reduce the likelihood of heart attacks. The Greenland Eskimo diet was nearly 100 percent fish. It is reasonable to assume that at a lower level of consumption of fish, some decrease in risk of heart attacks might occur even though not reaching nearly the practical immunity enjoyed by the Eskimos. Unfortunately, current research has made little attempt to address this problem. In most cases, in recent research the level of omega-3 fatty acids fed has been at very high levels sometimes approaching those in the diet of the Eskimos. This might require eating over a pound of fish per day or taking very considerable amounts of fish oil. In some instances where several levels of omega-3 fatty acids were fed, there has been some measurable decrease in platelet aggregation at the lower levels. This might or might not result in decreased risk of heart attacks.

In the case of the heart patients of Averly Nelson (Nelson, 1972) where those consuming fatty fish at least three times per week for periods of time from 16 to 19 years had only about 25 percent as many fatal heart attacks as in the control group, it seems likely that this difference could have been caused at least in part by a decreased level of platelet aggregation. Undoubtedly, if continued success is achieved in research now underway, experiments will be designed and carried out on effects of different levels of omega-3 fatty acids in the diet.

Literature Cited

- Barlow, S. M., and M. E. Stansby (editors). 1982. Nutritional evaluation of long-chain fatty acids in fish oils. Acad. Press, Lond., 318 p.
- Dyerberg, J. 1982. Observations on populations in Greenland and Denmark. In S. M. Barlow and M. E. Stansby (editors), Nutritional evaluation of long-chain fatty acids in fish oils, p. 245-261. Acad. Press, Lond.
- _____, H. O. Bang, S. Stoffersen, S. Moncada, and J. R. Vane. 1978. Eicosapentaenoic acid prevention of thrombosis and atherosclerosis. *Lancet* ii:117-119.
- Fisher, S., and P. C. Weber. 1984. Prostaglandin I₃ is formed *in vivo* in man after dietary eicosapentaenoic acid. *Nature* 307:165.
- Hirai, A., T. Hamazaki, T. Tenano, T. Nishikawa, Y. Tamura, A. Kumagai, and J. Sajiki. 1980. Eicosapentaenoic acid and platelet function in Japanese. *Lancet* ii:1141.

- Kobayashi, S., A. Hirai, T. Tenano, T. Hamazaki, Y. Tamura, and A. Kumagai. 1981. Reduction in blood viscosity by eicosapentaenoic acid. *Lancet* ii:197.
- Lands, W. E. M. 1982. Biochemical observations on dietary long-chain fatty acids from fish oil, and their effect on prostaglandin synthesis in animals and humans. *In* S. M. Barlow and M. E. Stansby (editors), *Nutritional evaluation of long-chain fatty acids in fish oil*. Acad. Press, Lond.
- _____, P. R. LeTellier, L. H. Rome, and J. Y. Vanderhoek. 1973. Inhibition of prostaglandin biosynthesis. *Adv. Biosci.* 9:15.
- Nelson, A. M. 1972. Diet therapy in coronary disease - effect on mortality of high-protein, high seafood, fat controlled diet. *Geriatrics* 27:103.
- Peifer, J. J., F. Janssen, P. Ahn, W. Cox, and W. O. Lundberg. 1960. Studies on the distribution of lipids in hypercholesterolemic rats. 1. The effects of feeding palmitate, linoleate, oleate, linolenate, menhaden, and tuna oils. *Arch. Biochem. Biophys.* 86:302.
- Sanders, T. A. B., and F. Roshanai. 1983. Influence of different types of omega-3 polyunsaturated fatty acids on blood lipids and platelet function in healthy volunteers. *Clin. Sci. Lond.* 64(1):91.
- Saynor, R., D. Vernal, and T. Gillot. 1984. Long-term effects of dietary supplementation with fish lipids on bleeding time, platelets and angina. *Altherosclerosis (Netherlands)* 50:3.
- Stansby, M. E. 1962. Proximate composition of fish. *In* E. Heen and R. Kreuzer (editors), *Fish in nutrition*, p. 55-60. Fish. News (Books) Ltd., Lond.
- _____. 1969. Nutritional properties of fish oils. *World Rev. Nutr. Diet.* 11:46.
- _____. 1973. Polyunsaturates and fats in fish. *J. Am. Diet. Assoc.* 63:625.