

# Fish consumption and omega-3-fatty acids in prevention of diet-related noncommunicable diseases

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## ABSTRACT

Diet-related noncommunicable diseases (DR-NCDs) which include obesity, hypertension, lipid disorders, type 2 diabetes mellitus, and cardiovascular (CV) disease are more common among people of South Asian descent because of genetic and other poorly understood factors. Indians are also one of the lowest consumers of fish and shellfish in the world despite being blessed with an extensive coastline. Consumption of fatty fish and fish oils supplementation has been demonstrated to improve blood pressure, lipid profiles, and CV outcomes. Data are still unclear if there is any impact on glucose intolerance with increased consumption of fatty fish or use of fish oils and omega-3-fatty acid (O3FA) supplements. The review focuses on the mechanisms of improvements with O3FAs on various aspects of DR-NCDs and reviews of current clinical data.

**Key words:** Cardiovascular disease, fatty fish, fish oils, noncommunicable diseases, omega-3-fatty acids

## INTRODUCTION

Diet-related noncommunicable diseases (DR-NCDs) include obesity, hyperlipidemia, glucose intolerant states including type 2 diabetes mellitus (T2DM), hypertension, and cardiovascular (CV) disease. DR-NCDs are more common among people of South Asian descent than many other racial groups. The reasons are likely to compose of genetics and additional poorly understood factors.<sup>[1]</sup> Currently, India has one of the largest numbers of patients with glucose intolerance and diabetes mellitus. A 10-year-old report from the World Health Organization in 2006 suggested that India was losing USD 9 billion worth of national income every year because of premature mortality and morbidity.<sup>[2]</sup>

It is assumed that the lower rates of CV disease and DR-NCDs among the Eskimos in Greenland and among the Japanese might be related to their higher per capita fish consumption. On an average, an Eskimo consumes over 400 g of fish a day while the average Japanese consumes about 100 g of fish a day.<sup>[3]</sup> This is in stark contrast to a per capita consumption of 3 kg of fish among an average Indian in a whole year as per data published in 2012. Consumption is much higher in coastal states (average 12 kg/year) and much lower in the noncoastal areas (2 kg/year). Even among the coastal states, cultural and religious factors play a role in consumption of fish with states such as Gujarat continuing to be low fish consuming despite being a major producer of marine fish.<sup>[4]</sup>

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Research in this field however has given inconsistent results over the years. Nevertheless, epidemiological, observational, and clinical trials have demonstrated myriad benefits of fish intake and in particular intake of fish oils in the primary and secondary prevention of CV disease.<sup>[5,6]</sup> This review attempts to summarize the current knowledge of the role of fish oils and other omega-3-fatty acids (O3FAs) in the primary and secondary prevention of CV disease and other DR-NCDs.

## OMEGA-3 FATTY ACIDS BIOCHEMISTRY

O3FAs are biological active compounds primarily derived from fish (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]).<sup>[7]</sup> Plant sources of O3FAs include the alpha-linolenic acid (ALA) containing flaxseeds, walnuts, canola oil, and chia seeds.<sup>[8]</sup> ALA can be converted to EPA and DHA in the human body by elongation and desaturation. Among fish, the oily fishes (tuna, mackerel, cod, herring, sardines, and salmon) are rich sources of O3FA.<sup>[9]</sup>

O3FAs belong to a class of essential long-chain highly unsaturated fatty acids consisting in addition to O3FA to O6FA. The classification of these fatty acids is given in Figure 1. All three of these fatty acids cannot be *de novo* synthesized in the human body and are hence termed essential fatty acids.<sup>[10]</sup>

## PROPOSED MECHANISMS BY WHICH OMEGA-3-FATTY ACIDS/FISH OILS IMPROVE NONCOMMUNICABLE DISEASE OUTCOMES

Experimental studies of O3FA on prevention and amelioration of NCDs have continuously expanded without sufficient clarity about the final mechanisms by

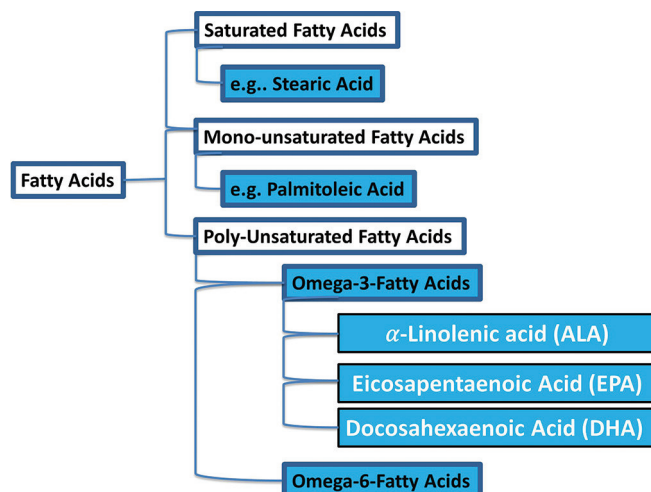


Figure 1: Classification of fatty acids

which they benefit. They most likely benefit via alteration of eicosanoid profiles, regulating gene expression, modulating membrane functions on cells and cell organelles, and changes in tissue metabolism.<sup>[11]</sup> These compounds have been clearly demonstrated to lead to changes in lipid profile, inflammatory milieu, lowering blood pressure, stabilizing atherosclerotic plaques, and improvement in glucose tolerance.<sup>[12]</sup>

### Blood pressure effects

Studies have indicated a modest decrease in systolic and diastolic blood pressures, with supplementation of O3FA. Mechanisms for blood pressure lowering might include augmentation of vagal tone which leads to improved autonomic functions, changes in cardiac electrophysiology, and improvements in the diastolic filling of the cardiac ventricles.<sup>[13]</sup> The effect on the vagal tone is likely to be of most importance as studies have suggested that fish consumption of 3 or more times a week was associated with reduction in heart rate by 3 bpm.<sup>[14]</sup>

Another potential mechanism of blood pressure lowering could relate to the antagonism of the vasoconstrictive effects of arachidonic acid-derived prostaglandins and thromboxanes. Prostaglandins derived from EPA/DHA such as lipoxins and resolvins antagonize the vasoconstricting prostaglandins and improve vascular tone. O3FAs appear to suppress the activity of angiotensin converting enzyme and lead to decreased production of angiotensin-2. O3FAs also improve the vasodilatory effects of endothelial nitric oxide.<sup>[15,16]</sup>

### Anti-inflammatory effects

Eicosanoids are arachidonic acid derivatives which promote inflammation and are derived from O6FAs. O3FAs intake reduces the production of eicosanoids and reduces inflammation and oxidative stress. The effect is only obvious with reasonably good intake of EPA/DHA of around 2 g a day.<sup>[17]</sup>

The primary prostaglandins derived from EPA and DHA are called resolvins (resolution phase interaction proteins). The resolvins possess potent anti-inflammatory action and exert direct immunomodulatory effects on neutrophils, dendritic cells, and macrophages.<sup>[18]</sup> These anti-inflammatory effects appear to have cardioprotective benefits though they do not appear to benefits disease with more significant inflammations such as arthritis and inflammatory bowel diseases.<sup>[18,19]</sup>

### Lipid effects

The consistent effects of O3FAs to reduce plasma triglycerides (TG) without increasing the low-density

lipoprotein cholesterol have been evident from epidemiological and clinical studies.<sup>[20]</sup> Fish oils reduce hepatic TG production via inhibition of hepatic enzyme synthesis responsible for TG synthesis and enhance the clearance of the circulation plasma TGs. A decrease in lipogenesis also decreases the availability of fatty acids for TG production.<sup>[20-22]</sup> Substantial reduction in TGs is seen when O3FAs are used in doses of 3–4 g/day.<sup>[23]</sup>

### Effect on glucose intolerance

Fish oils in modest doses do not appear to have any effect on insulin secretion (beta cell function) and insulin sensitivity in normal individuals.<sup>[24]</sup> In a prospective Chinese population-based cohort, an inverse relation was noted between intake of fish, shellfish, and long-chain fatty acids and T2DM in women.<sup>[25]</sup> These marine-based O3FAs were not associated with any increase in the risk of diabetes. A study involving middle aged woman who were prospectively followed up for 16 years suggested that intake of long chain fatty acids was associated with an increased risk of T2DM.<sup>[26]</sup> A Dutch study of adults above 55 years with no preexisting glucose intolerance also showed a positive relation between total fish intake and the risk of new-onset type 2 diabetes. EPA, DHA, and fatty fish intake was however not associated with the risk of diabetes, but the consumption of lean fish was thought to be a causative factor.<sup>[27]</sup>

Subsequent studies including a meta-analysis suggested that considerable study and statistical heterogeneity with significant geographical variations that make an accurate assessment of risk of diabetes with fish and fish oil intake difficult to interpret.<sup>[28]</sup> However it has been observed that South Asians appear to have a reduced risk of T2DM with consumption of fish and fish oils.<sup>[29]</sup>

### Effect on atherosclerosis

In addition to the indirect effects of O3FA and fish oils on atherogenesis mediated by the promotion of a pro-inflammatory milieu with antagonism of the anti-inflammatory O6FA-derived prostaglandins,<sup>[30]</sup> improvement in vascular tone by increasing nitrous oxide-mediated vasodilation and effects on the lipids and fish oils have direct effects on the processes that underlie atherogenesis.<sup>[16]</sup>

Primary among them is vascular smooth muscle proliferation, a decrease in plaque formation and stabilization of the fibrous cap of an atherosclerotic plaque prone to rupture.<sup>[31,32]</sup>

### Effect on biological aging and neurodegeneration

Recent research has suggested that fish oil consumption slows down biological aging by preserving telomere length.

A study carried in over 600 patients with stable heart disease showed that baseline O3FA levels in the plasma were found to be inversely proportional to the telomere shortening during 5 years of follow-up. Shortening of telomeres has previously been associated with poorer prognosis in patients with heart disease.<sup>[33]</sup>

Together with O6FAs, O3FAs constitute over 30–35% of total brain fatty acids. There is a suggestion that diets containing fish and fish oils may benefit cognition. Human studies however are not conclusive. A recent meta-analysis suggested that patients with dementia have lower blood levels of EPA and DHA.<sup>[34]</sup>

## CLINICAL STUDIES WITH OMEGA-3-FATTY ACIDS

Although individual studies suggested benefits of O3FA supplementation in the secondary prevention of CV events, recent systemic reviews and meta-analysis have not shown clear-cut benefits. Large trials of fish oil supplementation have yielded contradictory results.

The studies that favor O3FA in secondary prevention came with the following conclusions.

1. Geleijnse *et al.*<sup>[35]</sup> – higher intake (>0.5 g/day) of O3FA in older hypertensive patients independently reduces blood pressure
2. Burr *et al.*<sup>[36]</sup> – fatty fish intake causes 29% reduction in mortality after a recent myocardial infarction (MI) in men
3. Campos *et al.*<sup>[37]</sup> – consumption of plant-derived ALA reduces risk of recurrent MI in patients with previous MI
4. Yokoyama *et al.*<sup>[38]</sup> – EPA supplementation caused a 19% reduction in major CV events in patients with hypercholesterolemia
5. Bairati *et al.*<sup>[39]</sup> – patients on O3FA supplements undergoing primary angioplasty had less chances of restenosis
6. Calò *et al.*<sup>[40]</sup> – preoperative administration of O3FA in patients undergoing coronary artery bypass graft (CABG) improved postoperative outcomes including reduced risk of arrhythmias and reduced hospital stay
7. GISSi-HF study<sup>[41]</sup> – O3FA supplementation in patients with heart failure reduces mortality and hospitalization for heart failure.

On the other hand, studies that contradict the benefits of O3FA in ischemic heart disease came with these following conclusions.

1. Burr *et al.*<sup>[42]</sup> – two portions of oily fish/3 fish oil capsules daily caused a higher risk of cardiac death in men over the age of 70 years

2. Kromhout *et al.*<sup>[43]</sup> – low-dose EPA-DHA/ALA did not reduce CV events in patients with recent MI
3. Rauch *et al.*<sup>[44]</sup> – no significant decrease in arrhythmias or sudden cardiac death in patients with recent MI
4. Reis *et al.*<sup>[45]</sup> – the incidence of restenosis was found to be higher in the group that was supplemented with fish oils
5. Saravanan *et al.*<sup>[46]</sup> – polyunsaturated fatty acids administration before CABG did not change postoperative outcomes
6. Dijkstra *et al.*<sup>[47]</sup> – fish oils did not change outcomes in patients with heart failure
7. Belin *et al.*<sup>[48]</sup> – no association with EPA/DHA intake with outcomes in patients with heart failure.

Some of the reasons for these discordant results could be:

1. Patients from populations with high baseline fatty fish intake and high baseline O3FA levels do not seem to derive any additional benefit with supplementation
2. Many trials on secondary prevention were not long enough to make meaningful contributions
3. Patient included in recent trails with O3FA would receive far more aggressive optimal therapy with higher doses of statins and other cardioprotective medications that larger sample size with longer follow-up would be required for O3FA supplementation to show additional benefits.

## PHARMACOLOGICAL PREPARATIONS, DOSING, AND ADVERSE EFFECTS

For primary prevention of heart disease, the American Heart Association (AHA) recommends EPA and DHA intake of 0.5 g/day. This can be substituted for two or more servings of 3.5 oz servings of fatty fish at least twice a week. This appears to be a useful guide for the prevention of DR-NCDS as well.<sup>[49]</sup> The risk of glucose intolerance at this dosing is minimal. The American Diabetes Association has not recommended supplementation of O3FA in patients with diabetes but recommend that patients consume 2–3 oz servings of fish in a week.<sup>[50]</sup>

For secondary prevention in patients with established CV disease, the AHA recommends at least 1 g/day of EPA and DHA preferably sourced from seafood sources. In patients with hypertriglyceridemia, the recommended dosing is 2–4 g a day.<sup>[49]</sup>

Fatty fish in polluted environments may contain traces of mercury. Pregnant woman is probably better advised to avoid fatty fish and consume 0.3 g of pharmacological supplement of fish oil.<sup>[51]</sup>

Despite a large number of organizations with recommendations for fish oil intake, there still is no dietary reference intake (DRI) established for fish oils. A comprehensive DRI consisting of estimated average requirements, recommended daily allowance, adequate intake, and tolerable upper intake levels needs to be still established for this vital nutrient.<sup>[51]</sup>

The only adverse event noted in trials with higher doses (>4 g/day) was nausea. Patients occasionally complain of a fishy taste, especially with belching. Sourcing EPA/DHA from large fatty fish could in theory increase risk of mercury overdosing. This is more of concern in young children, pregnant, and lactating women.

## CONCLUSION

Fish consumption in our country is considerably lower than in other parts of the world despite our vast coastline and abundant marine resources. Even in coastal parts of our country, there has been a decline in the total consumption of fish in the last two decades. Fatty fish consumption, fish oils, and supplementation of O3FAs may be one of the ways for improving the DR-NCD profile of our country. Despite the risk of possible adverse effects on glucose intolerance, the benefits on lipids, blood pressure, and atherosclerotic disease far outweigh the risks.

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## Conflicts of interest

There are no conflicts of interest.

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