A FOCUS ON... omega-3 polyunsaturated fatty acids and the new Cochrane review

Alessandra Bordoni and Francesca Danesi

Background

The term ω-3 or n-3 describes a family of polyunsaturated fatty acids (PUFAs). The main types of n-3 PUFAs in human tissues and cells are α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is an essential fatty acid (FA) that can be found in foods such as walnuts, oilseeds (flax and rapeseed), and vegetable oils (rapeseed and soybean), and it cannot be synthesized by mammals. Humans can partially metabolize ALA by further desaturation and elongation into the n-3 long-chain polyunsaturated FAs (LC-PUFAs) EPA and DHA. The main source of n-3 LC-PUFAs in human nutrition is currently seafood, especially oily fish (salmon, sardines, and mackerel), and cod liver oil. DHA is also found in algae (1).

n-3 PUFAs are essential factors in many cellular functions such as regulating development, growth, and metabolism. They have been associated with benefits for the primary and secondary prevention of cardiovascular disease (CVD) (2–5). For these reasons, in recent years, much focus has been placed on increasing n-3 PUFAs consumption. The current Italian guidelines suggest consuming two to three servings of fish per week (6) (equivalent to ≈0.5 g/ day n-3 LC-PUFAs) required for primary prevention of CVD (7). A double amount of n-3 LC-PUFAs seems to be determinant in secondary prevention and can be reached only consuming supplements or fish oil (7, 8).

The new Cochrane review

The new Cochrane review published on July 18, 2018, in the Cochrane Library (9), assessed the effects of consuming n-3 LC-PUFAs for the primary and secondary prevention of CVD. It is a systematic review of 79 randomized controlled trials, which included 112,059 people and included the most recent research in this area. Trials were of 12 to 72 months' duration and included adults at varying cardiovascular risk, mainly in high-income countries (North America, Europe, Australia, and Asia). Most studies assessed n-3 LC-PUFA supplementation with capsules, but some used n-3 LC-PUFA- or ALA-rich or enriched foods compared to placebo or usual diet. Only a few studies have evaluated the effects of eating fish.

According to Cochrane review authors, only 25 of 79 studies were assessed as highly trustworthy because they were well designed and conducted. These evidenced that:

– increasing intake of n-3 LC-PUFAs provides little, if any, benefit on the risk of death from any cause (high certainty evidence);

– taking more n-3 LC-PUFAs mainly through supplements probably makes little or no difference to risk of cardiovascular events;

– n-3 LC-PUFAs slightly reduce serum triglycerides (high-quality evidence);

– n-3 LC-PUFAs slightly raise HDL cholesterol (HDL-C) (high-quality evidence); reducing HDL-C is likely to be not protective of heart diseases, although the association between high HDL-C and cardiovascular protection has recently been questioned (10);

– eating more ALA through food or supplements probably has little or no effect on cardiovascular deaths or deaths from any cause;

– eating more ALA probably reduces the risk of heart irregularities (from 3.3 to 2.6%);

– increasing n-3 LC-PUFAs or ALA probably does not affect body weight or fatness.

Some considerations

The review suggested that increasing intake of n-3 LC-PUFAs provides little, if any, benefit on most outcomes. Given the strong evidence from previous epidemiological studies (3, 4), this conclusion is somewhat surprising.

Most of the trials in this review included patients with pre-existing CVD, which is failing to differentiate between primary and secondary prevention and is a limitation when extrapolating recommendations for disease prevention in the general population. Tom Sanders, professor emeritus of Nutrition & Dietetics, King's College London, said that the review had a "major limitation" in that it has been unable to allow for the increased intakes of ω-3 FAs over the past 20 years because of changes in food production (11). This has occurred because the food industry increased the use of vegetable oils in processed foods, leading to higher intakes of ALA than in the past. Moreover, other important factors to consider are: (i) the different amounts of n-3 LC-PUFAs or ALA administered in the studies; (ii) the interaction between drug therapy and n-3 PUFA treatment; (iii) the variability of the diet among subjects.

Trial of dietary intervention differs from a trial with pharmacological treatment, where the magnitude of the drug effects is much higher than food effects. In addition, interindividual variations, due to genetic factors, can affect the absorption and metabolism of n-3 PUFAs as well as other nutrients or drugs (12, 13). A clustering of individuals based on genetic variation or, more easily, on erythrocyte phospholipid levels of n-3 PUFAs could explain the diverse physiological effects and allowing the development of individualized n-3 LC-PUFA recommendations (14) as in the case of folic acid (15).

Conclusion

Nutrition plays an important role in the prevention of CVD but establishing effects of specific nutritional components and their effective doses represent a complex issue. The Cochrane review suggests further studies

are needed to ensure a clinically meaningful answer in particular for secondary prevention. Although this conclusion needs to be taken into consideration, consumption of fish, preferably oily fish, at least twice a week remains a standard nutritional recommendation to maintain cardiovascular health in general populations.

References

1. Calder PC. Omega-3: The good oil. Nutrition Bulletin. 2017;42(2):132-140.
2. Poli A, Marangoni F, Visioli F. Alimentazione e prevenzione cardiovascolare: Recenti evidenze [The heart-friendly diet]. Giornale Italiano di Cardiologia. 2015;16(9):485-492.
3. Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: Evaluating the risks and the benefits. JAMA. 2006;296(15):1885-1899.
4. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Lancet. 1999;354(9177):447-455.
5. Russo GL. Dietary n-6 and n-3 polyunsaturated fatty acids: from biochemistry to clinical implications in cardiovascular prevention. Biochemical Pharmacology. 2009;77(6):937-946.
6. Istituto Nazionale di Ricerca per gli Alimenti e la Nutrizione. Linee guida per una sana alimentazione italiana: Ministero Politiche Agricole e Forestali; 2003. 84 pp.
7. Società Italiana di Nutrizione Umana. LARN. Livelli di assunzione di riferimento di nutrienti ed energia per la popolazione italiana. Milan: SICS; 2014. 656 pp.
8. Integratori Italia – AIIPA. Review scientifica sull'integrazione alimentare: Stato dell'arte alla luce delle evidenze scientifiche. Milan: EDRA; 2016. 104 pp.
9. Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. The Cochrane Database of Systematic Reviews. 2018;7:CD003177.
10. Allard-Ratick M, Khambhati J, Topel M, Sandesara P, Sperling L, Quyyumi A. Elevated HDL-C is associated with adverse cardiovascular outcomes. European Heart Journal. 2018;39(suppl_1):ehy564.550.
11. Thornton J. Omega 3 supplements do not reduce risk of heart disease, stroke, or death, finds review. BMJ. 2018;362.
12. Mancini M, Ordovas JM, Riccardi G, Rubba P, Strazzullo P. Nutritional and metabolic bases of cardiovascular disease: John Wiley & Sons; 2011. 488 pp.
13. Bordoni A, Astolfi A, Morandi L, Pession A, Danesi F, Di Nunzio M, et al. N-3 PUFAs modulate global gene expression profile in cultured rat cardiomyocytes. Implications in cardiac hypertrophy and heart failure. FEBS Letters. 2007;581(5):923-929.
14. von Schacky C. Omega-3 fatty acids in cardiovascular disease--an uphill battle. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2015;92:41-47.
15. Huo Y, Li J, Qin X, Huang Y, Wang X, Gottesman RF, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: The CSPPT randomized clinical trial. JAMA. 2015;313(13):1325-1335.