Omega-3: the Vanishing Nutrient beyond Cardiovascular Prevention and Treatment

Ronit Endevelt RD PhD[1,2] and Danit R. Shahar RD PhD[1]

[1]S. Daniel Abraham International Center for Health and Nutrition, Ben-Gurion University of the Negev, Beer Sheva, Israel
[2]Nutrition Unit, Maccabi Healthcare Services, Tel Aviv, Israel

Key words: omega-3, nutrition, docosahexaenoic acid, eicosapentaenoic acid

IMAJ 2004;6:235–239

Fatty acids of the w-3 and w-6 (n-6) series represent two distinct groups of fatty acids, both essential to humans and each with a significant physiologic role. These fatty acids are crucial because humans lack the ability to synthesize them *de novo*. At least two fatty acids, namely alpha-linolenic acid (18:3n-3) and linoleic acid (18:2n-6), must be supplied by the diet as precursors. Humans can synthesize other essential fatty acids – such as docosahexaenoic acid (22:6n-3), eicosapentaenoic acid (20:5n-3) and arachidonic acid (20:4n-6) – from these precursor fatty acids via desaturation and elongation pathways that are shared by both n-3 and n-6 fatty acids. n-3 fatty acids are involved in a variety of physiologic processes, including retina and brain function, modulation of eicosanoid action and transcriptional regulation of gene expression [1]. Eicosanoids derived from arachidonic acid are pro-inflammatory and pro-aggregatory agonists, whereas those derived from n-3 polyunsaturated fatty acids tend to inhibit platelet aggregation and can be anti-inflammatory. n-3 long chain PUFA suppress production of pro-inflammatory cytokines and cartilage degradative enzymes [2], both being important components of nearly all cell membranes and affecting cell membrane fluidity [3].

In this issue of *IMAJ* Weisman and colleagues [4] discuss omega-3 fatty acid supplementation for primary and secondary prevention of coronary heart disease. We would like to add to the important findings of their review, and widen the vision on the influence of omega-3 on health and disease beyond the cardiovascular field. In our literature search for relevant articles we found more than 7000 articles written in the last 5 years.

The lack of omega-3 in the food chain: a historical view

In the early 1970s observational studies suggested that omega-3 fatty acids may reduce the occurrence of myocardial infarction-related deaths in Greenland Eskimos. These Eskimos represent a natural reservation of human ancestral eating habits. Since the 1970s additional trials have supported this finding [5].

The human diet today is vastly different from that of our ancestors. For early mankind, hunting, fishing and food gathering were a survival imperative and, as a consequence, humans evolved on 'natural' foods that supplied a diet low in total fat and saturated fat, containing a balance of omega-6 and omega-3 essential fatty acids. For the major part of human existence on earth, we have eaten foods containing omega-6 and omega-3 at a ratio of about 2:1. In recent centuries, the emphasis gradually moved away from hunting and gathering towards cultivating the land, but the greatest diet changes occurred in the past 50 years. As a result of our increasing reliance on cereals, processed foods and, most significantly, vegetable oils and spreads, compounded by a decreased consumption of oily fish and grass-fed meat, today the ratio of foods containing omega-6 and omega-3 is about 10–20:1. Modern western diets are therefore deficient in omega-3 fatty acids compared with the diet on which humans evolved and on which our genetic patterns were established. The increased use of intensive, cereal-based livestock production systems in the western world has resulted in a lower proportion of n-3 fatty acids in meat as compared with traditional, more extensive production systems. Overall, there has been a shift in the balance between n-6 and n-3 fatty acids over the past 30 years. This shift is reflected in the declining concentrations of DHA and rising concentrations of linoleic acid in breast milk and in the meat we eat [6]. Changes in food production in the western world have led to a decrease in omega-3 consumption. Concern about the health of people has prompted interest in the health characteristics of various kinds of foods with special attention to omega-3, which is becoming increasingly rare in the American diet [7].

Another issue regarding omega-3 derived from fish is that of contamination. Research comparing the mercury content of fish with that of fish-oil tablets showed that although fish are rich in omega-3 fatty acids and their consumption is recommended to decrease the risk of coronary artery disease, fish such as swordfish and shark are a source of exposure to the heavy metal toxin, mercury. The fish-oil brands examined in that study were found to contain negligible amounts of mercury and therefore may provide a safer alternative to fish consumption [8]. Table 1 presents the omega-3 content of selected sea foods. Since the omega-3 content varies markedly depending on species, season, diet, and packing and cooking methods, the figures are rough estimates.

Research that was done on yellow cheese from cows fed freely in the Alps showed that cheese made from the milk of these cows had

PUFA = polyunsaturated fatty acids

DHA = docosahexaenoic acid

Table 1. Content of omega-3 in selected seafoods*

Seafoods	Amount of fish (in g) required to provide 1 g EPA +DHA	EPA+DHA content (g) per 100 g serving of fish
Tuna (fresh)	66–357	0.28–1.51
Atlantic salmon	42.5–70.9	1.28–2.15
Mackerel	54–250	0.4–1.85
Atlantic herring	50	2.01
Rainbow trout	87	1.15
Sardines	50–87	1.15–2
Halibut	85–213	0.47–1.18
Tuna (canned)	323	0.31
Cod	357	0.28
Haddock	417	0.24
Catfish	556	0.18
Flounder or sole	204	0.49
Oysters	227	0.44
Seafood	313	0.32
Tuna (fresh)	500	0.2

* Adapted from the guidelines of the American Heart Association) [9]

a better fatty acid profile than all other cheese types. Alpine cheese may be a relevant source of ALA (alpha-linolenic acid, n3), a fact that may explain the Alpine cardiovascular paradox [10]. Most of the food that animals in the western world eat today lacks the ability to convert into omega-3 fatty acids. As a result, the meat and animal products that we currently eat also lack omega-3.

Omega 3 in the newborn infant

Studies on non-human primates and human newborns indicate that DHA is essential for the normal functional development of the retina and brain, particularly in premature infants. Because omega-3 fatty acids are essential for growth and development throughout the life cycle, they should be included in the diets of all humans. Omega-3 and omega-6 fatty acids are not interconvertible in the human body, yet are important components of practically all cell membranes. Whereas cellular proteins are genetically determined, the polyunsaturated fatty acid composition of cell membranes is largely dependent on dietary intake [11].

Among neonates, DHA status correlates positively with birth weight, birth length and head circumference. Therefore, maternal DHA supplementation during pregnancy may improve the prognosis of preterm infants. In term neonates, maternal linoleic acid consumption correlates negatively with neonatal head circumference, suggesting that the ratio of omega-3 fatty acid to omega-6 PUFAs in the maternal diet should be increased. Consumption of trans-unsaturated fatty acids appears to be associated with lower maternal and neonatal PUFA status. It therefore seems prudent to minimize the consumption of trans-fatty acids during pregnancy and increase the consumption of DHA and EPA [12]. Omega-3 was also found to be essential for brain and vision development during the last 3 months of pregnancy and continues to play a major health role at every stage.

EPA = eicosapentenoic acid

The effect of omega-3 fatty acids on bipolar disorder and depression

Lower dietary intake of seafood was shown in several studies [13] to be related to a higher prevalence of affective disorders. Hibbeln [14] reported that greater seafood consumption was related to a lower lifetime prevalence rate of major depression across nine countries (r = -0.84, $P < 0.005$). Frequent fish consumption, twice a week or more, was an independent factor for a reduced risk of depressive symptoms (odds ratio 0.57) in a restricted geographic region within a single country [15]. Additionally, and consistent with these findings, several reports showed lower plasma concentrations of EPA and DHA among depressed compared with healthy subjects [16,17]. A recent cross-sectional analysis of seafood consumption found that greater seafood consumption predicted lower lifetime prevalence rates of bipolar disorders with a vulnerability threshold below 50 lb (22.5 kg) per person per year [18].

One placebo-controlled clinical trial of patients with bipolar disorder treated with omega-3 supplements reported a marked reduction in depressive symptoms over 4 months of treatment [19]. A recently published 4 month small-scale study compared fish oil-derived omega-3 fatty acids (6.2 g EPA and 3.4 g DHA per day) to olive oil for patients suffering from bipolar disorder. Patients in the omega-3 group had significantly longer periods of remission than those who received placebo.

The mechanism that links fish consumption and depression may be the regulation of serotonergic nervous system function. Lower serotonergic activity has been well established in the pathophysiology of depression. High cerebrospinal fluid concentrations of 5-hydroxy-indoleacetic acid, a metabolite of serotonin and an indicator of brain serotonin turnover, have been shown to be associated with high plasma concentrations of omega-3 PUFA among healthy subjects [20]. A decrease in fish intake would lead to a higher proportion of omega-6 and a lower proportion of omega-3 in the cell membranes of most tissues. These alterations in the cell membranes may lead to changes in membrane microviscosity and, hence, in the neurotransmitter systems implicated in depression [17]. As for bipolar disorder, it has been suggested that bipolar disorders may be caused by overactivity of cell signal transduction [21]. High dose therapy with omega-3 fatty acids leads to the incorporation of these components into the cell membrane [22]. This inhibits neural signal transduction pathways in a similar manner to lithium and sodium valproate (treatment for bipolar mood disorders). Thus far, the results of studies on the effect of omega-3 treatment for depression and bipolar disorders indicate a promising therapy. Longer intervention studies with larger populations are required to confirm this action.

W-3 fatty acids and schizophrenia

In 1977 Horrobin [23] proposed the membrane phospholipids hypothesis as the cause of schizophrenia. According to this hypothesis a prostaglandin deficiency, possibly caused by defective enzyme systems for converting dietary essential fatty acids into omega-6 fatty acids, prostaglandin precursors, arachidonic and gamma-dihomolinolenic acid, was implicated in schizophrenia [24]. It has been suggested that prostaglandins, particularly PGE1, may

modulate dopaminergic neurons [25]. In a subsequent study in 1998, Horrobin suggested that there was an accelerated loss of the essential fatty acids DGLA, EPA, AA and DHA from phospholipid neuronal membrane in schizophrenics [26]. This loss may lead to changes in cell signaling and the functioning of membrane-associated proteins.

There are also substantial data suggesting that the metabolism of both omega-3 and omega-6 are disrupted in schizophrenia [27]. Levels of AA and DHA in the red blood cell membranes of drug-treated schizophrenics were found to be particularly reduced [28]. Another study showed that patients with mainly negative symptoms had significantly reduced levels of AA and DHA [24].

The effect of fatty acid supplementation on schizophrenic symptoms was reported only in clinical trials. One study, divided into two parts, involved 20 patients with chronic schizophrenia [25]. Dietary intake of omega-3 fatty acids, particularly EPA, was associated with fewer schizophrenic symptoms, especially positive symptoms, and a decrease in the symptoms of tardive dyskinesia. The study found no relationship between RBC omega-3 fatty acid content and the symptoms of schizophrenia. There was a significant positive correlation between RBC omega-6 fatty acid content and poor clinical readings according to the results of two scales – PANSS (Positive and Negative Syndrome Scale) and AIMS (Abnormal Involuntary Movement Scale). A multivariate analysis revealed that a larger intake of omega-3 fatty acids was related to fewer positive symptoms of schizophrenia and a lower incidence of tardive dyskinesia after adjusting for confounding factors. High levels of omega-6 fatty acids in RBC membranes resulted in more negative symptoms. Another study used omega-6 supplements [29]. In the 38 patients who completed the trial, the low levels of fatty acids in RBC membranes, particularly linoleic acid, AA and DHA, appeared to be related directly to the severity of tardive dyskinesia. No improvement was demonstrated on the AIMS scale. The authors concluded that the RBC membranes of psychiatric patients (primarily schizophrenics) had lower levels of most omega-6 and omega-3 fatty acids [29].

The results of two other clinical trials were also published in the last 3 years [30]. In one study patients with schizophrenia received daily doses of 2 g EPA and no change in antipsychotic treatment. The study showed significant improvement in most indicators for change. The percentage reduction in the negative subscale was 49% ($P < 0.05$) and the percentage reduction in the positive subscale 30% ($P < 0.01$). The second study included a treatment group that received 2 g of DHA daily. There was significant improvement in the positive symptoms scale and the total PANSS but only in the EPA group. Both EPA and DHA had no significant effect on negative symptoms.

It cannot be claimed unequivocally that fatty acid supplementation is an effective treatment for schizophrenia. Nonetheless, despite the conflicting results of the few published studies, the overall results are promising. Clearly, there is an urgent need for clinical trials to either confirm or refute the efficacy of omega-3 fatty acids in the treatment of mental disorders.

AA = arachidonic acid
RBC = red blood cells

Omega 3 and cardiovascular disease

Patients in primary care prevention with combined hyperlipidemia are at risk for activation of the coagulation system, particularly during postprandial lipemia. This activation may be significantly reduced by statins and omega-3. As shown in several studies, when compared with statins taken alone [30], omega-3 fatty acids lower serum triglycerides in both women (pre- and postmenopause) and men [31].

Epidemiologic and clinical trial data suggest that omega-3 may reduce the risk of cardiovascular related death by 29–52%. In addition, the risk of sudden cardiac death decreased by 45–81% [5]. Possible mechanisms for these beneficial effects include anti-arrhythmic properties, improved endothelial function, anti-inflammatory action and reductions in serum triglyceride concentrations.

Omega-3 fatty acids are fairly well tolerated. Potential adverse effects include bloating and gastrointestinal distress, "fishy taste" in the mouth, hyperglycemia, an increased risk of bleeding and a slight increase in low density lipoprotein cholesterol [5].

Among patients with coronary heart disease, a literature search identified randomized controlled trials that compared dietary or non-dietary intake of n-3 PUFA with a control diet or placebo [32]. Studies had to have at least 6 months of follow-up data and to have reported clinical endpoint data. We identified 11 trials, published between 1966 and 1999, that included 7,951 patients in the intervention and 7,855 patients in the control groups. The results showed that the risk ratio of non-fatal myocardial infarction in patients on n-3 PUFA-enriched diets, compared with control diets or placebo, was 0.8 (95% confidence interval 0.5–1.2, $P = 0.16$; Breslow-Day test for heterogeneity, $P = 0.01$) and the risk ratio of fatal myocardial infarction was 0.7 (95% CI 0.6–0.8, $P < 0.001$; heterogeneity $P > 0.20$). In five trials, sudden death was associated with a risk ratio of 0.7 (95% CI 0.6–0.9, $P < 0.01$; heterogeneity $P > 0.20$), whereas the risk ratio of overall mortality was 0.8 (95% CI 0.7–0.9, $P < 0.001$; heterogeneity $P > 0.20$). There was no difference in further estimates between dietary and non-dietary interventions of n-3 PUFA for all endpoints. To summarize, omega-3 fatty acids may be beneficial and should be considered in patients with documented coronary heart disease; they may be particularly helpful for patients with risk factors for sudden cardiac death [32]. In their thorough review in the current issue of *IMAJ* [4], Weisman and co-authors provide crude evidence for secondary prevention of cardiovascular disease with the aid of omega-3.

Is there an Israeli paradox: the omega-3/omega-6 ratio?

Research in Israel reveals that the Israeli population consumes a high level of omega-6 fatty acids while the intake of omega-3 fatty acids is relatively low. There is a debate in the literature as to whether the ratio itself or the amount in total is crucial for the health benefits of omega-3. Moreover, the recommended amount of omega-3 content for human tissues that will provide health benefits is unknown [33].

CI = confidence interval

The relevance of omega-3 to diseases in the modern world

Clinical trials have demonstrated that EPA and DHA in the form of fish oils, and in conjunction with anti-rheumatic drugs, ameliorate joint pain in patients with rheumatoid arthritis; have a beneficial effect in patients with ulcerative colitis; and in combination with other drugs heal skin lesions; lower the level of hyperlipidemia from exterminates; and decrease the toxicity of cyclosporin in patients with psoriasis. Several of the placebo-controlled trials of fish oil for treating chronic inflammatory diseases revealed significant benefits, including decreased disease activity and a reduced use of anti-inflammatory drugs [34]. In addition, according to the Cochrane Library, it seems that omega-3 fatty acid plays as an important role in several evidence-based reviews. In accordance with the biochemical effects, beneficial anti-inflammatory effects of dietary fish oils have been demonstrated in randomized, double-blind, placebo-controlled trials in rheumatoid arthritis [2].

Immuno-nutrition based on dietary supplements enriched with arginine, glutamine and omega-3 fatty acid (fish oil) led to a better recovery in patients with Injury Severity Scores (ISS) of 15–30 and burn patients at Siriraj Hospital, Bangkok, with a body surface area of 30–60%, rather than the use of a conventional nutritional supplement [35].

A new model for cancer prevention, based on anti-inflammatory agents, suggests a positive correlation between omega-3 consumption and a decrease in cancer manifestation in tissue *in vitro* tests [36]. In various animal studies omega-3 fatty acids decreased the number and size of tumors and increased the time that elapsed before the reappearance of tumors. Epidemiologic and other studies suggest that a diet rich in omega-3 essential fatty acids may have beneficial anti-inflammatory effects in chronic conditions such as cystic fibrosis. The review of trials found that regular omega-3 supplements may help people with cystic fibrosis, with relatively few adverse effects, although the evidence is insufficient to draw firm conclusions that would recommend routine use of omega-3 supplements [37].

Summary

Omega-3 appears to be an important nutrient component of the mammalian body, however because of changes in the food chain during the last century it has become increasingly rare in frequently eaten foods. Currently, the main source of omega-3 is fish, which tends to be expensive and is periodically found to be contaminated. Common foods such as eggs, chicken, etc., which were once a rich source of omega-3, are now lacking it. Given the importance of omega-3 in a variety of body functions, as well as in the prevention of disease, it is obvious that in the coming years the scientific community worldwide will have to target agricultural research and development to the enrichment of foods with omega-3.

References

1. Nakumara M, Nakamura T. The return of w3 fatty acids into the food supply: land-based animal food products and their health effects. *World Rev Nutr Diet* 1998;83:1998.
2. Cleland LG, James MJ, Proudman SM. The role of fish oils in the treatment of rheumatoid arthritis. *Drugs* 2003;63(9):845–53.
3. Lee KW, Lip GYH. The role of omega-3 fatty acids in the secondary prevention of cardiovascular disease. *QJM* 2003;96(7):465–80.
4. Weisman D, Motro M, Schwammenthal E, et al. Efficacy of omega-3 fatty acid supplementation in primary and secondary prevention of coronary heart disease. *IMAJ* 2004;6:227–32.
5. Carroll DN, Roth MT. Evidence for the cardioprotective effects of omega-3 fatty acids. *Ann Pharmacother* 2002;36(12):1950–6.
6. Sanders TA. Polyunsaturated fatty acids in the food chain in Europe. *Am J Clin Nutr* 2000;71(Suppl 1):176–8S.
7. Plotnikoff GA. Food as medicine – cost-effective health care? The example of omega-3 fatty acids. *Minn Med* 2003;86(11):41–5.
8. Foran SE, Flood JG, Lewandrowski KB. Measurement of mercury levels in concentrated over-the-counter fish oil preparations: is fish oil healthier than fish? *Arch Pathol Lab Med* 2003;127(12):1603–5.
9. Kris-Etherton PM, Harris WS, Appl LJ, for the nutrition committee. AHA scientific statement. Fish consumption, fish oil, omega 3 fatty acid and cardiovascular disease. *Circulation* 2002;106:2747–57.
10. Hauswirth CB, Scheeder MR, Beer JH High omega-3 fatty acid content in alpine cheese: the basis for an alpine paradox. *Circulation* 2004;109(1):103–7. Epub 2003 Dec 15.
11. Simopoulos A. Essential fatty acids in health and chronic disease. *Am J Clin Nutr* 1999;70:560–9S.
12. Hornstra G. Essential fatty acids in mothers and their neonates. *Am J Clin Nutr* 2000;71:1262–S9.
13. Hibbeln JR, Salem N Jr. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy [Review]. *Am J Clin Nutr* 1995l;62(1):1–9.
14. Hibbeln JR. Fish consumption and major depression. *Lancet* 1998;351: 1213.
15. Tanskanen A, Hibbeln JR, Hintikka J, Haatainen K, Honkalampi K, Viinamaki H. Fish consumption, depression, and suicidality in a general population. *Arch Gen Psychiatry* 2001;58(5):512–13.
16. Edwards R, Peet M, Shay J, Horrobin D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J Affect Disord* 1998;48(2-3):149–55.
17. Maes M, Smith R, Christophe A, Cosyns P, Desnyder R, Meltzer H. Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J Affect Disord* 1996;38(1):35–46.
18. Noaghiul S, Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. *Am J Psychiatry* 2003; 160(12):2222–7.
19. Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56(5):407–12.
20. Hibbeln JR, Linnoila M, Umhau JC, Rawlings R, George DT, Salem N Jr. Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. *Biol Psychiatry* 199815;44(4):235–42.
21. Stoll AL, Severus WE. Mood stabilizers: shared mechanisms of action at postsynaptic signal-transduction and kindling processes. *Harv Rev Psychiatry* 1996;4(2):77–89.
22. Sperling RI, Benincaso AI, Knoell CT, Larkin JK, Austen KF, Robinson DR. Dietary omega-3 polyunsaturated fatty acids inhibit phosphoinositide formation and chemotaxis in neutrophils. *J Clin Invest* 1993; 91(2):651–60.
23. Horrobin DF. Schizophrenia as a prostaglandin deficiency disease. *Lancet* 1977;i:936–7.
24. Maidment ID. Are fish oils an effective therapy in mental illness? An analysis of the data. *Acta Psychiatr Scand* 2000;102(1):3–11.
25. Horrobin DF. The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. *Schizophr Res* 1998;30(3):193–208.

26. Laugharne JD, Mellor JE, Peet M. Fatty acids and schizophrenia. *Lipids* 1996;31(Suppl):S163–5.
27. Mellor JE, Laugharne JD, Peet M. Schizophrenic symptoms and dietary intake of n-3 fatty acids. *Schizophr Res* 1995;18(1):85–6.
28. Vaddadi KS, Courtney P, Gilleard CJ, Manku MS, Horrobin DF. A double-blind trial of essential fatty acid supplementation in patients with tardive dyskinesia. *Psychiatr Res* 1989;27(3):313–23.
29. Peet M, Brind J, Ramchand CN, Shah S, Vankar GK. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophr Res* 2001;49(3):243–51.
30. Nordoy A, Svensson B, Hansen JB. Atorvastatin and omega-3 fatty acids protect against activation of the coagulation system in patients with combined hyperlipemia. *J Thromb Haemost* 2003;1(4):690–7.
31. Stark KD, Park EJ, Maines VA, Holub BJ. Effect of a fish-oil concentrate on serum lipids in postmenopausal women receiving and not receiving hormone replacement therapy in a placebo-controlled, double-blind trial. *Am J Clin Nutr* 2000;72:389–94.
32. Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med* 2002;112(4):298–304.
33. Dubnov G, Berry EM. Omega-6/omega-3 fatty acid ratio: the Israeli paradox. *World Rev Nutr Diet* 2003;92:81–91.
34. Campos FG, Waitzberg DL, Teixeira MG, Mucerino DR, Kiss DR, Habr-Gama A. Pharmacological nutrition in inflammatory bowel diseases. *Nutr Hosp* 2003;18(2):57–64.
35. Chuntrasakul C, Siltham S, Sarasombath S, et al. Comparison of a immunonutrition formula enriched arginine, glutamine and omega-3 fatty acid, with a currently high-enriched enteral nutrition for trauma patients. *J Med Assoc Thai* 2003;86(6):552–61.
36. Wallace JM. Nutritional and botanical modulation of the inflammatory cascade – eicosanoids, cyclooxygenases, and lipoxygenases – as an adjunct in cancer therapy. *Integr Cancer Ther* 2002;1(1):7–37.
37. Beckles Willson N, Elliott TM, Everard ML. Omega-3 fatty acids (from fish oils) for cystic fibrosis. Cochrane Review 2003;4.

Correspondence: Dr. R. Endevelt, Nutrition Unit, Maccabi Healthcare Services, 27 Hamered Street, Tel Aviv 68125, Israel.
Phone: (972-3) 514-3755
email: ronit_a@mac.org.il