REVIEW

Clinical Impact of Omega-3 Consumption on the Management of Chronic Heart Failure

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Abstract
Interest in omega-3 has grown dramatically since the observation that Eskimos have a high level of omega-3 due to high fish consumption that was associated with a low incidence of myocardial infarction. This was thought to be related to its antithrombotic effect due to inhibition of platelet aggregation. Subsequently, several studies indicated a potential beneficial impact of omega-3 in the treatment and prevention of cardiovascular disease including chronic heart failure (CHF) especially in patients with reduced ejection fraction. Despite the progress in the medical and device management of CHF, a significant number of patients with this clinical syndrome do not respond to current therapy. In addition, CHF remains a condition of a high morbidity, hospitalization and mortality. Therefore, clinicians got interested in exploring any potential benefit in the care of patients with CHF. Potential benefits of omega-3 in the management of CHF patients have been evaluated and showed possible positive effect on the progression of CHF through several mechanisms. These include the improvement of endothelial function, reduction of vascular tone, reduction of platelet aggregability, and improvement of myocardial function. This review article cites data from several experiments pertaining to the benefits of omega-3 in patients with CHF. The aim is to review the mechanisms, potential benefits, and possible therapeutic implications of omega-3 in patients with CHF. Results show that there is a significant difference in patients who intake omega-3 versus those who do not. This article is proof that there are other methods to treating CHF than what is prescribed in modern medicine.

Keywords: Chronic heart failure, Omega-3, platelet aggregation, arrhythmia

Introduction

Chronic Heart failure (CHF) is considered amongst the most

cause of hospitalization in patients older than 65 years and one of the leading causes of death in advanced countries (1). According to the American Heart Association (AHA) update in 2013, it is estimated that 5.1 million people in United States were affected by CHF in 2006 (2). Leading risk factors are ischemic heart disease, hypertension, diabetes mellitus, myocardial infarction and valvular heart disease. However, omega-3 has shown potential benefits on cardiovascular risk factors (3). This association was first observed and reported in the 1940s. This was particularly noted in people who consume a high quantity of fish and exhibit low cardiovascular mortality (4). Over the past three decades, epidemiologic and experimental data have provided evidence of the beneficial effect of omega-3 in preventing CHF.

Omega-3 fatty acids are among the most commonly prescribed supplements with a remarkable worldwide market. In 2011, people spent around $25 billion on omega-3 supplements. This amount is estimated to approach $35 billion in 2016 (40). Omega-3 fatty acids are a class of unsaturated fatty acids that consist of multiple sites for double bonds, one of which is on the third carbon, also known as the omega carbon end of the chain (41). Types of omega-3 acids include eicosapentaenoic acid (EPA) with 20 carbons, and docosahexaenoic acid (DHA), with 22 carbons. EPA and DHA are mainly gained from seafood consumption. However, small amounts of EPA and DHA can also be synthesized in the body using alpha linolenic acid (ALA), an 18-carbon omega-3 fatty acid found in plants such as flaxseed, canola and walnuts (42). Docosapentaenoic acid (DPA) is another long chain of omega-3 fatty acid and is a metabolite of DHA. DPA is thought to be formed through internal metabolic pathways rather than dietary intake.

The effects of omega-3 include reduction in blood pressure, triacylglycerol levels, and heart rate variability. The latter effects occurs as a result of an augmentation of vagal tone, modulation of adrenergic-mediated baroreceptor activity, and improvement in sinoatrial node function with reduction of erratic sinus firing (5,6). In addition, consumption of high quantity of omega-3 could reduce arrhythmia (7); improve survival in patients who has a myocardial infarction (8); reduce inflammation and improved endothelial function in CHF patients (9). Heart failure (HF) is a complex clinical syndrome with multiple etiologies. Current treatment options can slow the progression to HF, but overall the prognosis remains poor. Clinical studies suggest that high dietary intake of the omega-3 polyunsaturated fatty acids (omega-3PUFA) may lower the incidence of HF, and that supplementation with pharmacological doses prolongs event-free survival in patients with established HF. The mechanisms for these potential benefits are complex and not well defined. Several trials tested the hypothesis that omega-3 fatty acids reduce fatal coronary artery diseae (CAD) and sudden death. The first meta-analysis of these trials was published in 2002 (43) followed by others (44, 45). However, several meta-analyses included not only trials in which the effect of omega-3 fatty acids in fish oils was investigated but also trials in which a fish advice or margarines enriched with ALA were given (46). This review aims to appraise and summarize this ever-increasing volume of published work and present it to the practicing physicians, whom will consider Omega 3 supplement in specific patients with CHF.

Methods

We searched the PubMed database using keywords "Omega -3" in title or "n-3" in title and "heart" in all fields. Out of 878 hits, we filtered the search to only 167 clinical trials and papers. Our team screened the titles and abstracts of the 167 articles and only included articles that were published between 1982 and 2013 and are relevant to cardiac function including lipid metabolism, electrophysiology, arrhythmia, blood pressure control, platelet function and inflammation as well as vascular function. Therefore, 126 out of 167 articles were reported for full text review. Out of these accepted articles, there were a total amount of 194414 patients studied, 30919 of which were male and 33303 of which were female. 109 out of the 126 studies consisted of random samples and 17 of the experiments contained a placebo group of patients without CHF (Table 1).

Results

We will review the above literature in special order according to the natural history of CHF. We will discuss the preventive impact of omega -3 on pre-CHF cardiovascular risk factors that could prevent from the development of cardiomyopathy and clinical CHF. Then, we will discuss the therapeutic impact of omega 3 on clinical CHF.

Preventive effects of omega-3 on pre-CHF cardiovascular risk factors

Omega-3 has suggested positive preventive effects on a number of different physiologic mechanisms of the cardiovascular system, including lipid metabolism, blood pressure control, platelet function, and vascular function.

Table 1. Characteristics of studies included

Characteristics	Records
Total Participants Studied	194414
Males Reported	30919
Females Reported	33303
Studies with Control Groups	17

Lipid metabolism

Several studies have demonstrated potent triglyceride-lowering effect of Omega-3 in both normolipidemic (triglyceride < 200 mg/dL) and hyperlipidemic subjects (triglyceride ≥ 200 mg/dL). One study demonstrated a 25% reduction in triglyceride level in normolipidemic subjects and 25–34% in hyperlipidemic subjects when subjects consumed 3–4 gram of omega-3 a day. However, the higher the baseline triglycerides level the higher the lowering effect of Omega-3 (10). Balk et al demonstrated same effect of omega-3 in healthy, diabetic, hypertensive, dyslipidemia or CAD subjects (11).

There is no significant effect of omeg-3 on HDL cholesterol or total cholesterol concentration; however, other studies reported an increase in the larger HDL particles that are preventive of cardiac event (10, 11). There is conflicting data regarding the effect of omega-3 on the LDL levels. Mori et al showed no significant change in LDL-cholesterol concentration but reported that LDL particles large, more buoyant and less atherogenic than small LDL that are synthesized in the body (12). Huff et al and Telford et al reported 5% and 10% increase in LDL cholesterol in normolipidemic and hyperlipidemic individuals respectively (13). Yokoyama et al reported 10% reduction in LDL concentration. Co-administration of omega-3 with statins is safe and has additive effects on plasma lipids (14, 15).

Heart rate and blood pressure

Omega-3 has moderate effects on reducing the heart rate and blood pressure. The average heart rate decreases by 2.5 beats per minute after 12 weeks of omega-3 consumption (16). The lowering effect of omega-3 on blood pressure [average of 5.8 mmHg of systolic and 3.3 mmHg of diastolic (5)] is related to an increased in membrane stabilization and decreased sensitivity to electrical excitability of the sympathetic nervous tone (16).

Recently, a potential new indication of omega-3 fatty acids has been demonstrated, that is heart failure. In the GISSI-HF trial (47); a placebo-controlled trial of approximately 7000 patients with class II to IV heart failure, the patients were randomized to 1 g of omega-3 fatty acids (containing 850–882 mg of EPA plus DHA), rosuvastatin (10 mg), both of them, or dual placebo. This study was performed in addition to well-established current therapies, and the results showed a significant benefit of omega-3 fatty acids. However, the optimal dose of omega-3 fatty acids remains to be determined depending on different stages and/or aetiology of heart failure and underlying mechanisms (48). Growing evidence demonstrates anti-inflammatory effects of omega-3 fatty acids, including reduced circulating levels of inflammatory cytokines and AA-derived eicosanoids, and elevated plasma adiponectin. In animal studies, fish oil favorably alters cardiac mitochondrial function (49). All of these effects may work together to prevent the development and progression of heart failure.

Platelet function and clotting factors

Omega-3 may reduce the risk of thrombosis by affecting platelet aggregation. Omega-3 competes with cyclooxygenase activity with arachidonic acid, which lowers platelet aggregation. Administration of omega-3 is associated with 30% reduction of platelet aggregation (17). Other studies have shown that omega-3 reduces the levels coagulation factors, namely VII and X (18) and fibrinogen levels (19).

Vascular function

Omega-3 has a direct negative effect on atherosclerotic plaques progression by lowering the infiltration of macrophage (20). Omega-3 also decreases vascular proliferation and tone, which are important factors

of atherosclerosis. Omega-3 enhances the production of endothelium derived relaxing factor that improve endothelial dysfunction atherosclerotic vessels (21). This results in vasodilatation and improved coronary artery flow (22). The endothelium derived relaxing factor also inhibits platelet aggregation and adhesion, smooth muscle cell proliferation and leukocyte adhesion (21, 22). The effect of omega-3 inhibits vascular proliferation via several signaling pathways (23).

Atrial fibrillation

Atrial fibrillation (AF) could result is cardiomyopathy due to irregularities as well as tachycardia-induced cardiomyopathy. Therefore, upstream intervention to prevent from AF or to treat AF in patients with CHF with omega-3 has been evaluated. Multiple studies showed no association between the risk of developing AF and dietary fish intake rich in omega-3 (24-27). Mozaffarian et al evaluated fish intake rich in omega-3 and the risk of incidence of AF. The study showed that there is a decrease in incidence of AF amongst those who consume fish. However, this study exclusively looked at subject's ≥ 65 years of age (28). Omega-3 showed preventive effect in cardiac surgery patients. A small, randomized and controlled study of 160 post-bypass patients was performed to assess the benefits of omega-3 on the development of postoperative AF (29). The results from this study were remarkably in support of omega-3 oil (18.1% absolute risk reduction and 54.4% relative risk reduction). These results compare favorably to the results of another large meta-analysis (58 studies including 8,565 participants) (30), which examined the effects of amiodarone, sotalol, and beta-blockers on post-bypass AF. In comparison, the results of studies that utilized omega-3 supplementation in post-bypass patients seem to be similar or even superior to those that used the list of other treatments for prevention of AF. But further large-scale studies are needed, with some currently underway (31), to assess the impact of different doses of omega-3 oil and its role in primary and secondary prevention of AF.

Therapeutic effects of omega-3 in clinical CHF

The investigators of a major CHF study (GISSI-HF study), evaluated the effect of omega-3 in patients with CHF. There was a reduction in mortality and hospitalization for cardiovascular reasons in patients with CHF whom consumed omega-3 (8). This therapeutic effect of omega-3 was also noted in doxorubicin-induced CHF in rats (32). This effect was thought be related to omega-3 antiarrhythmic and CHF progression effect (7). As mentioned above, the GISSI-HF trial sought to objectively assess the efficacy of omega-3 supplement in patients with CHF. The subject pool was composed of 60% CHF patients and 40% with a history of MI. The majority of patients treated with guideline derived medical therapy (GDMT) CHF regimen, including angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin II receptor blockers, and spironolactone. However, only 22% of the patients were on a statin. Same investigators of the GISSI-HF re-evaluated omega-3 in another study as an add-on therapy to 10mg daily of rosuvastatin. Omega-3, but not rosuvastatin, significantly decreased death or admission to a hospital for cardiovascular reasons (33).

CHF patients are prone to ventricular arrhythmia (VA) and sudden cardiac death (SCD). In vitro studies, omega-3 has shown an antiarrhythmic effect but the data are not conclusive (34). Several studies assessed the effect of omega-3 on heart rate variability (HRV) as a measure of cardiovascular autonomic function and the risk of SCD.

These studies showed that the consumption of tuna or fish oil in patients with cardiomyopathy and CHF was associated with reduction of mean heart rate by 13.6%; reduction of the resting heart rate; improvement of the heart rate recovery post-exercise; and increased the HRV in men with history of MI and left-ventricular dysfunction (EF less than 40%); shorter QT interval; improvement of T-wave alternans signal; reduction of ventricular arrhythmia and SCD (5, 34-36). The GISSI Prevention trial evaluated the effect of Omega-3 on SCD. The GISSI prevention trial showed that treatment with omega-3 was associated with reductions in risk of SCD in patients that had a myocardial infarction within the past three months (37).

Consumption of omega-3 in patients with CHF and an implantable cardioverter defibrillator (ICD) showed minimal effect on VA in ICD in few studies (38, 39) whereas only one study showed a potent effect of omega-3 on reducing VA in ICD patients (28). Therefore, the effect of omega-3 on preventing VA is controversial. Omega-3 fatty acids (n-3 PUFA) preparations differ in composition and dose. Only preparations with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as ethyl esters of at least 85% (850 mg/g) have shown an effect on the cumulative endpoint of cardiovascular death and hospitalization. No effect of n-3 PUFA preparations containing, 850 mg/g has been shown in either HFrEF or post-myocardial infarction

n-3 PUFA preparations containing 850–882 mg of EPA and DHA as ethyl esters in the average ratio of 1:1.2 may be considered as an adjunctive therapy in patients with symptomatic HFrEF who are already receiving optimized recommended therapy with an ACEI (or ARB), a beta-blocker and an MRA (50,51).

Conclusions

In summary, dietary supplementation with omega-3 might exert preventive effects of pre-CHF cardiovascular risk factors including lipid metabolism, heart rate, blood pressure, platelet aggregation, clotting factor, vascular function, endothelial dysfunction and arrhythmia especially AF. Therefore, omega-3 supplementation could be considered in patient with CAD, myocardial infarction, hyperlipidemia as an add-on therapy or in case of allergic reaction to statin. The beneficial effect of omega-3 in patients with clinical CHF is supported by findings of the GISSI-HF trial, which reported substantial reductions in overall mortality and hospitalization. Therefore, omega-3 might add incremental benefits to the current guideline derived medical therapy (GDMT) of CHF. Omega-3 antiarrhythmic property is still considered a debate, but could be an attractive option as an adjunct to the standard antiarrhythmic drugs in patients with AF, VA, SCD and ICD.

Several issues remain to be elucidated. First, no evidence has been found for the optimal dosage, ratios of DHA to EPA, and ratios of omega-3 to omega-6. Second, whether dietary intake or therapeutic supplements are the best source of omega-3 fatty acids is yet to be determined. These issues remain to be clarified in future studies.

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References

1. Roger VL, Go AS, Lloyd DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics-2011 update: A report from the American Heart Association. Circulation 2011;123(4):e18-e209.
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics- 2013 update: A report from the American Heart Association. Circulation 2013;127(1):e6-e245.
3. Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. et al. Eicosapentaenoic acid and prevention of thrombiosis and atherosclerosis?. Lancet 1978;2:117-9.
4. Sinclair HM. Deficiency of essential fatty acids and atherosclerosis, etcetera. Lancet 1956;270:381-3
5. Mozaffarian D, Prineas RJ, Stein PK, Siscovick DS. Dietary fish and n-3 fatty acid intake and cardiac electrocardiographic parameters in humans. J Am Coll Cardiol 2006;48(3):478-84.
6. Mozaffarian D, Stein PK, Prineas RJ, Siscovick DS. Dietary fish and omega-3 fatty acid consumption and heart rate variability in US adults. Circulation 2008;117(9):1130-7.
7. Leaf A, Kang JX, Xiao YF, Billman GE. Clinical prevention of sudden cardiac death by omega 3 polyunsaturated fatty acids and mechanism of prevention of arrhythmias by omega 3 fish oils. Circulation 2003;107:2646-52
8. GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999;354:447-55.
9. Lennie TA, Chung ML, Habash DL and Moser DK. Dietary fat intake and pro-inflammatory cytokine levels in patients with heart failure. J Card Fail 2005;11(8):613-8.
10. Harris WS. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 1997;65(suppl):1645S-54S.
11. Balk EM, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis 2006;189(1):19-30.
12. Mori TA, Burke V, Puddey IB, Watts GF, O'Neal DN, Best JD, et al. Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. Am J Clin Nutr 2000; 71(5):1085-94.
13. Edwards IJ, Gebre AK, Wagner WD, Parks JS. Reduced proteoglycan binding of low density lipoproteins from monkeys (Macaca fascicularis) fed a fish oil versus lard diet. Arterioscler Thromb 1991;11(6):1778-85.
14. Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Ishikawa Y, et al Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis 2008; 200(1):135-140.

15. Davidson MH, Stein EA, Bays HE, Maki KC, Doyle RT, Shalwitz RA, et al. COMBOS investigators. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8- week, randomized, double-blind, placebo controlled study. Clin Ther 2007;29(7):1354-67.
16. Kang JX. Reduction of heart rate by omega-3 fatty acids and the potential underlying mechanisms. Front Physiol 2012 Oct 30;3:416.
17. Larson MK, Ashmore JH, Harris KA, Vogelaar JL, Pottala JV, Sprehe M, et al. Effects of omega-3 acid ethyl esters and aspirin, alone and in combination, on platelet function in healthy subjects. Thromb Haemost 2008;100(4):634-41
18. Oosthuizen W, Vorster HH, Jerling JC, Barnard HC, Smuts CM, Silvis N, et al. Both fish oil and olive oil lowered plasma fibrinogen in women with high baseline fibrinogen levels. Thromb Haemost 1994;72(4):557-62
19. Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European concerted action on thrombosis and disabilities angina pectoris study group. N Engl J Med 1995;332(10):635-41.
20. Shahar E, Folsom AR, Wu KK, Dennis BH, Shimakawa T, Conlan MG. Associations of fish intake and dietary n-3 polyunsaturated fatty acids with a hypocoagulable profile. The Atherosclerosis Risk in Communities (ARIC) Study. Arterioscler Thromb 1993;13(8):1205-12.
21. Israel DH, Gorlin R. Fish oils in the prevention of atherosclerosis. J Am Coll Cardiol 1992;19(1):174-85.
22. Fleischhauer FJ, Yan WD, Fischell TA. Fish oil improves endothelium-dependent coronary vasodilation in heart transplant recipients. J Am Coll Cardiol 1993;21(4):982-9
23. Terano T, Shiina T and Tamura Y. Eicosapentaenoic acid suppressed the proliferation of vascular smooth muscle cells through modulation of various steps of growth signals. Lipids 1996;31(suppl):S301-4.
24. Leaf A. Prevention of sudden cardiac death by n-3 polyunsaturated fatty acids. Fundam Clin Pharmacol 2006; 20(6):525-38.
25. Brouwer IA, Heeringa J, Geleijnse JM, Zock PL, Witteman JC. Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation. The Rotterdam Study. Am Heart J 2006;151(4):857-62.
26. Frost L, Vestergaard P. n-3 fatty acids consumed from fish and risk of atrial fibrillation or flutter: the Danish Diet, Cancer and Health Study. Am J Clin Nutr 2005;81(1):50-4.
27. Leo´n H, Shibata MC, Sivakumaran S, Dorgan M, Chatterley T, Tsuyuki RT. Effect of fish oil on arrhythmias and mortality: systematic review. BMJ 2008;337:a2931.
28. Brouwer IA, Zock PL, Camm AJ, Böcker D, Hauer RN, Wever EF et al. Effect of fish oil on ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators: the study on omega-3 fatty acids and ventricular arrhythmia (SOFA) randomized trial. JAMA 2006;295(22):2613-9.
29. Mozaffarian D, Psaty BM, Rimm EB, Lemaitre RN, Burke GL, Lyles MF et al. Fish intake and risk of incident atrial fibrillation. Circulation 2004;110(4):368-73.
30. Calò L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, et al. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery. J Am Coll Cardiol 2005;45(10):1723-8.
31. Crystal E, Garfinkle MS, Conolly SS, Ginger TT, Sleik K, Yusuf SS. et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database Syst Rev 2004;(4): CD003611.
32. Teng LL, Shao L, Zhao YT, Yu X, Zhang DF, Zhang H. The beneficial effect of n-3 polyunsaturated fatty acids on doxorubicin-induced chronic heart failure in rats. J Int Med Res 2010;38(3):940-8.
33. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. Lancet 2008; 372(9645):1223-30
34. Panagiotakos DB, Lionis C, Zeimbekis A, Makri K, Bountziouka V, Economou M, et al. Long-term, moderate coffee consumption is associated with lower prevalence of diabetes mellitus among elderly non-tea drinkers from the Mediterranean islands (MEDIS study). Rev Diabet Stud 2007;4(2):105-11.
35. Mozaffarian D, Prineas RJ, Stein PK and Siscovick DS. Dietary fish and n-3 fatty acid intake and cardiac electrocardiographic parameters in humans. J Am Coll Cardiol 2006;48(3):478-784.
36. Nodari S, Metra M, Milesi G, Manerba A, Cesana BM, Gheorghiade M, et al. The role of n-3 PUFAs in preventing the arrhythmic risk in patients with

idiopathic dilated cardiomyopathy. Cardiovasc Drugs Ther 2008;23(1):5-15.
37. Ghio S, Scelsi L, Latini R, Masson S, Eleuteri E, Palvarini M, et al. Effects of n -3 polyunsaturated fatty acids and of rosuvastatin on left ventricular function in chronic heart failure: a substudy of GISSI-HF trial. Eur J Heart Fail. 2010;12(12):1345-53.
38. Leaf A, Albert CM, Josephson M, Steinhaus D, Kluger J, Kang JX, et al. Prevention of fatal arrhythmias in high-risk subjects by fish oil Omega 3 fatty acid intake. Circulation 2005;112(18):2762-8.
39. Raitt MH1, Connor WE, Morris C, Kron J, Halperin B, Chugh SS, et al. Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators. JAMA 2005;293(23):2884-91.
40. Schultz H. Retail omega-3s sales to hit $34.7 billion in 2016, report predicts. 2012. Available from: http://www.nutraingredients-usa.com/Markets/Retail-omega-3s-sales-to-hit-34.7-billion-in-2016-report-predicts [cited 2016 October 20];
41. Weylandt KH, Chiu CY, Gomolka B, Waechter SF, Wiedenmann B. Omega-3 fatty acids and their lipid mediators: towards an understanding of resolvin and protectin formation. Prostaglandins Other Lipid Mediat 2012;97(3-4):73-82.
42. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 2011;58(20):2047-67.
43. 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.
44. Zhao YT, Chen Q, Sun YX, Li XB, Zhang P, Xu Y, et al. Prevention of sudden cardiac death with omega-3 fatty acids in patients with coronary heart disease: a meta-analysis of randomized controlled trials. Ann Med. 2009;41(4):301-10.
45. Hooper L, Thompson RL, Harrison RA, Summerbell CD, Ness AR, Moore HJ et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. BMJ 2006;332(7544):752-60.
46. Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. Clin Cardiol 2009; 32(7):365-72.
47. Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Gissi-HF Investigators Lancet 2008;372(9645):1223-30.
48. Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. J Am Coll Cardiol 2009;54(7):585-94.
49. Duda MK, O'Shea KM, Stanley WC. Omega-3 polyunsaturated fatty acid supplementation for the treatment of heart failure: mechanisms and clinical potential. Cardiovasc Res 2009;84(1):33-41.
50. Lucas M, Kimmig M, Karalis G. Do omega-3 polyunsaturated fatty acids prevent cardiovascular disease? A review of the randomized clinical trials. Lipid Insights 2013;6:13-20.
51. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37(27):2129-200.