Progress in Cardiovascular Diseases xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Health: A Comprehensive Review☆

Andrew Elagizi [a], Carl J. Lavie [b,*], Keri Marshall [c], James J. DiNicolantonio [d], James H. O'Keefe [d], Richard V. Milani [b]

[a] Department of Internal Medicine, Leonard J Chabert Medical Center, Houma, LA
[b] Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, the University of Queensland School of Medicine, New Orleans, LA
[c] Director Global Lipid Science and Advocacy for DSM Nutritional Products, Columbia, MD
[d] Mid America Heart Institute at Saint Luke's Hospital, Kansas City, MO

ARTICLE INFO

Available online xxxx

Keywords:
Omega 3 polyunsaturated fatty acid
Omega 3 index
Omega 6
Cardiovascular disease
Coronary heart disease
Heart failure
Heart transplant
Sudden cardiac death
Myocardial infarction

ABSTRACT

The potential cardiovascular (CV) disease (CVD) benefits of Omega-3 Polyunsaturated Fatty Acids (OM3) have been intensely studied and debated for decades. Initial trials were performed in patients with low use of maximal medical therapy for CVD, and reported significant mortality benefits with the use of 1 g/day OM3 intervention following myocardial infarction (MI). More recent studies, including cohorts of patients receiving modern guideline directed medical therapy for CVD, have often not shown similar benefits with OM3 use. We conducted a literature review using PubMed, professional society guidelines, specific journal databases including *New England Journal of Medicine* and *Journal of the American College of Cardiology* from January 1, 2007 to December 31, 2017. References from selected articles were also reviewed, as well as key articles outside of the selected timeframe for their important findings or historical perspectives.

Currently, there are no Class I recommendations from the American Heart Association (AHA) for the use of OM3, however, considering the safety of this therapy and beneficial findings of some modern studies (including patients with current maximal medical therapy for CVD), the AHA has recently expanded their list of Class II recommendations, in which treatment with OM3 for CVD benefit is reasonable. This review discusses the current state of the evidence, summarizes current professional recommendations, and provides recommendations for future research.

Contents

Abbreviations and acronyms: AF, atrial fibrillation; AHA, American Heart Association; AHRQ, Agency of Healthcare Research and Quality; ALA, alpha-linolenic acid; ASA, aspirin; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; DM, diabetes mellitus; EPA, eicosapentaenoic acid; FDA, Food and Drug Administration; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; LVSVI, left ventricular systolic volume index; MACE, Major Adverse Cardiovascular Events; MI, myocardial infarction; OM3, Omega-3 polyunsaturated fatty acid; OM6, Omega-6 polyunsaturated fatty acid; RCT, randomized controlled trial; RLP, remnant lipoprotein; SCD, sudden cardiac death; SDA, stearidonic acid; TG, triglyceride.

☆ Statement of Conflict of Interest: see page XX.

* Address reprint requests to Carl J. Lavie, John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, 1514 Jefferson Highway, New Orleans, LA 70121-2483.
E-mail address: clavie@ochsner.org (C.J. Lavie).

https://doi.org/10.1016/j.pcad.2018.03.006
0033-0620/

Please cite this article as: Elagizi A, et al. Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Health: A Comprehensive Review. *Prog Cardiovasc Dis* (2018), https://doi.org/10.1016/j.pcad.2018.03.006

The potential role of Omega-3 polyunsaturated fatty acids (OM3) in reducing cardiovascular (CV) disease (CVD) and CVD events has been studied for decades. As early as 1944, Sinclair[1] described the rarity of coronary heart disease (CHD) in Greenland Eskimos, who consumed a diet high in whale, seal and fish. While there are many well-known physiologic benefits of consuming fish or fish oil supplements, and multiple CV benefits demonstrated in several studies, there remains much controversy regarding the relationship between OM3 and CV health.

Current guidelines from the American Heart Association (AHA) recommend 2 servings of fatty fish per week for the general population,[2] and state that it may be reasonable to recommend fish or fish oil capsules (1 g/day OM3) for CVD risk reduction as secondary prevention for patients with CHD and other atherosclerotic vascular disease.[3] More recently, the AHA concluded that OM3 treatment is reasonable for (I) secondary prevention of CHD death, (II) patients with heart failure (HF) with reduced ejection fraction (HFrEF), and (III) secondary prevention of CHD in patients with a recent CHD event, such as recent myocardial infarction (MI).[4] The purpose of this review is to evaluate the current evidence regarding OM3 and CV health, explain potential benefits and uses of OM3 and make recommendations for future research.

Biochemistry and sources of OM3

Biologically relevant families of the polyunsaturated fatty acids are the Omega-6 (OM6) and OM3.[5] The major OM3 include alpha-linolenic acid (ALA, primarily in plants), eicosapentaenoic acid and docosahexaenoic acid (EPA and DHA, respectively, both primarily in marine life), and others such as stearidonic acid (SDA) and docosapentaenoic acid (DPA) are present in very low amounts in the diet.[6] ALA is found only in trace amounts in green leafy vegetables, but is found in larger quantities in plants and seeds as well as plant and seed oils such as flaxseed (also known as linseed), chia, soybean, walnuts and other tree nuts, and olive oil and rapeseed (canola) oils.[5,7] Although ALA can be converted to EPA with subsequent conversion of EPA to DHA, this conversion is complex and limited.[5] In general, humans convert <5% ALA to EPA and even less (0–4%) ALA to DHA.[7,8] Some studies suggest possible CV benefits of ALA, but the evidence is mixed and inconclusive overall.[8] Therefore, plant based OM3 cannot be considered a replacement for marine based OM3, specifically EPA and DHA. However, further study for the health benefits of ALA is important because of abundant global supply.[8]

EPA and DHA enter the food chain through marine phytoplankton or algae, and humans mainly obtain these OM3 from consuming fish, particularly oily fish, such as mackerel, trout, salmon, herring, albacore tuna and sardines.[5,7] Fish do not naturally produce these oils, but obtain them from consuming marine microorganisms in their natural diet.[7] Therefore, OM3 are typically found in higher levels in wild fish, as farmed fish are often grain fed, and the OM3 in fish are not synthesized de novo, but stem from unicellular organisms at the base of their natural food chain (Fig. 1).[9]

"Stealth health" is a concept in which intrinsically enhancing OM3 content of meat from chickens and other monogastric animals such as pigs seems readily achievable, and these "stealth health" foods could be an ideal mechanism for delivering OM3 without changing dietary habits.[10] Also, transgenic animals that express the fat-1 gene from the worm *Caenorhabditis elegans* have been raised, and this gene encodes an OM3 fatty acyl desaturase that converts OM3 substrates into OM3; the supplementation with meat from these transgenic animals might permit enrichment of mammalian cells with OM3.[5] These methods may one day be used to improve the OM3 status of those whom are deficient, and without the need for dietary changes.

OM3 index

One objective measure of an individual's OM3 status is the OM3 index, which measures the OM3 content in red blood cell membranes (Fig. 2).[11] An OM3 index < 4% has been associated with increased CHD risk, particularly sudden cardiac death (SCD), whereas an index > 8% is considered low risk for CHD and 4–8% is intermediate risk.[11] It has been argued that a low OM3 index could serve as a novel CVD risk factor, and can also be used to reclassify individuals from intermediate CVD risk to low or high risk groups.[12] Many previous OM3 intervention trials have yielded neutral results, and it has been proposed that incorporating the OM3 index into trial designs to understand baseline OM3 levels, and treating to a target (e.g. 8–11%) will make more efficient trials and treatment possible.[12]

The OMEGA-REMODEL trial suggested that the OM3 index may serve as a useful marker of treatment efficacy,[13] and it has also been shown that the Global Registry of Acute Coronary Events score had an improved c-statistic and correctly reclassified a significant proportion of patients by the inclusion of fatty acids.[14] We have previously argued that the inadmissibility of memory recall as scientific evidence limits the use of many nutritional studies, which may explain why the relation of

Please cite this article as: Elagizi A, et al. Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Health: A Comprehensive Review. *Prog Cardiovasc Dis* (2018), https://doi.org/10.1016/j.pcad.2018.03.006