Omega-3 Polyunsaturated Fatty Acids

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Omega-3 polyunsaturated fatty acids (Ω-3) confer cardiovascular (CV) benefits through Triglyceride (TG) reduction, anti-inflammatory and anti-arrhythmic effects, vasodilation, reduced blood pressure, improved arterial and endothelial function, favorable autonomic tone, and reduced platelet aggregation

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1. Introduction

As early as 1944, Sinclair described the rarity of coronary heart disease (CHD) amongst Greenland Eskimos, who consumed a diet rich in fish, seal and whale [1]. More than 40 years ago, Bang and Dyerberg reported that despite low consumption of fruit, vegetables and complex carbohydrates in exchange for a diet high in saturated fat and cholesterol, serum cholesterol and triglyceride (TG) levels were lower in Greenland Inuit than in age-matched residents of Denmark, who also demonstrated lower risk of myocardial infarction (MI) [2]. These and other similar observations sparked interest in the potential benefits of increased dietary fish intake, particularly the benefits of omega-3 polyunsaturated fatty acids (Ω-3), for cardiovascular (CV) health.

Ω-3 confer CV benefits through TG reduction, anti-inflammatory and anti-arrhythmic effects, vasodilation, reduced blood pressure, improved arterial and endothelial function, favorable autonomic tone, and reduced platelet aggregation [3][4][5]. In particular, TG levels are a historically well-studied, independent risk factor for CHD. Ω-3 or fish oil diet supplementation is evidenced to lower TG levels in a dose-dependent fashion, whereby 3–4 g/day of eicosapentaenoic acid (EPA) or a combined EPA and docosahexaenoic acid (DHA) reduces blood levels by 20–50% in those with high TGs [6].

2. Ω-3 Index

One aspect that has been lacking from this field of research for a long time, however, is a concerted methodology of measurement. Hereto now, most research has utilized average fish consumption or arbitrary supplement dosing, often not considering the source of Ω-3 or the individual's initial or concluding Ω-3 blood levels. The Ω-3 index is a measurement of serum Ω-3 levels (EPA + DHA), with multiple potential uses in research and clinical practice. The Ω-3 index has been proposed as an indicator of increased CHD risk when <4% [6], which also coincidently reflects the estimated average American serum level of Ω-3 [7]. An individual is at low risk when their Ω-3 index is >8% [8][9]; and studies have shown that achieving an Ω-3 index > 8% can potentially reduce the risk of fatal CHD by approximately 35% [7][10]. A large meta-analysis of global studies using biomarkers of Ω-3 in 45,637 patients without CHD revealed that higher Ω-3 levels are strongly correlated with lower incidence of fatal CHD [11]; this is an inverse relationship whereby higher Ω-3 levels are associated with lower risk of CHD in a continuous gradient fashion. Just as hemoglobin A1c is the clinical standard for assessing glycemic status, the Ω-3 index is a superior method for evaluating long-term Ω-3 status [7]. Adequate diagnostics for indicating Ω-3 intake is critical to ensuring a personalized approach to prescribing EPA and DHA for an individual to achieve health outcomes. For clear reasons, this index can also be used as a target in clinical trials to reduce heterogeneity in trial design. Effective use of the Ω-3 index as a clinical diagnostic and research tool may be the key to resolving the controversy surrounding Ω-3 therapy.

3. Heart Failure

The benefits of Ω-3 have also been studied in heart failure (HF) patients, and the most impressive study focusing on Ω-3 in this population was the GISSI-HF trial [10]. This study, conducted in Italy, involved 1 g/day Ω-3 (EPA + DHA) or placebo in nearly 7000 HF patients (91% with reduced ejection fraction (HFrEF)) followed for a median of 3.9 years. Not only did this trial confirm the safety of Ω-3 in HF patients, but also found a NNT of 56 over 3.9 years to prevent one death or NNT of 44 to avoid one death or hospital admission for CVD reasons. Based on the results of GISSI-HF, the American Heart Association (AHA) provides a class IIa indication that Ω-3 treatment is reasonable among patients with HFrEF [11].

However, the AHA guidelines do not provide recommendations for Ω-3 use in the primary prevention of HF due to a lack of data [11]. A meta-analysis of 7 prospective studies with 176,441 subjects and 5480 incident cases of HF found a lower risk of HF with higher intake of marine Ω-3 (Relative risk 0.85; 95% CI, 0.73–0.99, p = 0.04) [12]. Block et al. [13]. measured EPA levels in 6,562 patients over 13 years, finding that plasma EPA levels were significantly lower in HF patients compared to HF-free patients (p = 0.005), and this benefit was noted among patient groups with either preserved or reduced ejection fractions. The possibility that increased Ω-3 may reduce HF incidence warrants further study. An AHA scientific advisory suggests a general dietary recommendation for 1–2 fish servings per week to prevent HF [14].

Not only is it possible that Ω-3 can reduce HF incidence, Ω-3 may be beneficial in end-stage HF as well. A small study of 14 patients with New York Heart Association class III–IV HF received 8 g of Ω-3 vs. placebo for 18 weeks, showing a significant 59% reduction in tumor necrosis factor-α (TNF-α) levels, and 39% decrease in interleukin-1 (IL-1), and body weight increase (due to decreased cachexia), whereas the placebo group demonstrated a significant 44% increase in TNF-α and no change in IL-1 [15]. While underpowered, these findings show promise that Ω-3 may represent a novel therapeutic approach in treating end-stage HF with cachexia. These mechanisms of decreased inflammation may explain the beneficial findings of GISSI-HF.

Effects of Ω-3 have also been studied extensively in various forms of CVD, with several studies demonstrating improvements in CVD risk factors, including atherosclerosis, atrial and ventricular arrhythmias, hyperlipidemia, peripheral arterial disease and ischemic stroke [3]. An extensive discussion regarding the benefits of Ω-3 therapy for these conditions is beyond the scope of this article and has been discussed previously [3][4][11]. Studies regarding Ω-3 and HF have been emphasized here due to recent HF guidelines suggesting that Ω-3 treatment is reasonable among HFrEF patients, and mounting evidence that suggests Ω-3 may be beneficial in reducing HF incidence as well.

4. Molecular Mechanisms

The mechanisms responsible for the CVD benefits of Ω-3 intake have not been clearly established, though recent research provides new insights. Some CVD Benefits from Ω-3 therapy may be attributable to metabolites which are potent anti-inflammatory mediators. For example, the resolvin E series of metabolites are synthesized from EPA and actively reduce leukocyte tracking to the site of inflammation, promote the clearance of inflammatory cells and suppress cytokine production [16]. Multiple animal studies have shown the benefits of these anti-inflammatory mediators post-myocardial infarction [17]. Administration of resolvin E1 attenuates the infarct size in rats subject to ischemia/reperfusion injury and resolvin D1 induces a switch to anti-inflammatory M2 macrophages in the left ventricle to prevent myocardial fibrosis [18] [19].

In addition to anti-inflammatory effects, Ω-3 may reduce arrhythmias via direct inhibition of sarcolemmal ion channels which may stabilize electrical activity and prolong the relative refractory period of the cardiomyocytes [20]. Anti-arrhythmic effects have been demonstrated in both animal as well as human studies. EPA dose dependently reduced pulmonary vein spontaneous beating and the amplitude of delayed afterdepolarizations in rabbit tissue [21]. Prolonged atrial refractoriness has been shown in humans with Ω-3 supplementation (6 g/day EPA + DHA for at least 1 month) with reduced vulnerability to induce atrial fibrillation [22], though trials such as STRENGTH and REDUCE-IT showed increased rates of atrial fibrillation. It is possible that higher doses, such as 6 g/day, may be needed for some anti-arrhythmic effects. Ω-3 also improve endothelial function by increasing nitric oxide production by directly stimulating endothelial nitric oxide synthase gene and protein expression [23]. Ongoing research regarding these molecular pathways is required to better understand the CVD benefits of Ω-3.

5. Conclusions

The Ω-3 index is an objective measurement of endogenous Ω-3 levels, specifically for EPA and DHA, and can be used to evaluate: baseline Ω-3 status, response to Ω-3 therapy, as a clinical target for CV health and, if used consistently in clinical trials, can make future study more easily interpretable and comparable. Effective implementation of diagnostics for Ω-3, including use of the Ω-3 index as a clinical and research tool, may be the key to resolving much controversy surrounding the efficacy of Ω-3 therapy.

Multiple trials continue to use an Ω-3 intervention dose of 1 g/day of EPA + DHA, which demonstrated significant CVD benefits in the landmark GISSI-P trial. However, trials demonstrating a benefit with this low dose, such as GISSI-P, GISSI-HF and JELIS, were performed in Italian and Japanese populations with higher baseline Ω-3 intake in their regular diet, which may account for their ability to reach a therapeutic level of Ω-3 which confers CVD benefits. The efficacy of modern

medical therapy for CVD can further confound the benefits of Ω-3 supplementation due to reduced overall CVD events. Patients in Western nations or nations with lower Ω-3 intake in general may require higher-dose interventions (e.g., 2–4 g/day of EPA + DHA) to reach a therapeutic effect of Ω-3.

Several decades and countless dollars have been spent studying the relationship between Ω-3 and CVD without reaching a consensus among clinicians. There is, however, clear evidence from multiple studies that higher doses of Ω-3 (2–4 g/day of EPA + DHA) appear to be safe and to reduce CVD events in multiple CVD populations, which warrants further study to conclusively determine the potential benefits of this safe, inexpensive, and well-tolerated therapy.

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