Fish Oil Dilemma: Does It Increase the Risk of Ventricular Arrhythmias and Death? Can Fish Oil Kill You?

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Abstract: Omega-3-fatty-acids are now increasingly being used for potential beneficial anti-inflammatory effect in the treatment and management of cardiovascular disease. Eicosapentaenoic acid and Docosahexaenoic acid are 2 essential omega-3 fatty acids found predominately in fish and fish oil supplements. Despite the increased use of fish oil products for both primary and secondary prevention of cardiovascular morbidity and mortality, the available literature evidence are controversial. We searched through PubMed for studies that have investigated the impact of omega-3 fatty acids on coronary heart disease and mortality. Our systemic review suggests that most studies, which are mostly observational, have found there to be a potential benefit of omega-3 fatty acids on coronary heart disease whereas some other studies have found conflicting results. More randomized controlled studies are warranted with adequate sample size to clearly establish the risk and benefits of omega-3 fatty acids on cardiovascular disease. (Curr Probl Cardiol 2021;46:100718.)

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Introduction

Omega-3-fatty-acids, or fish oil with its main biologically important components, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) are being utilized for cardiovascular disease prevention. Both EPA and DHA are essential fatty acids which are not synthesized by the human body. Primary sources of these 2 dietary omega-3-fatty-acids are seafood products such as fish and fish oil.[1,2] Thirty-eight percent of all deaths in the United States are attributed to cardiovascular disease, many of which are preventable.[3] Multiple studies have shown that persistently elevated levels of inflammatory markers such as C-reactive protein, TNF-alpha, and some ILs (IL-1, IL-6) are associated with an increased incidence of cardiovascular events.[4-6] EPA and DHA are thought to have anti-inflammatory effect and play a role in oxidative stress on the cells.[4,7] The cardio-protective effect polyunsaturated-omega-fatty-acids (PUFA) has been of interest starting from the early 1930s. Initial observation of lower rates of myocardial infarction (MI) in the Inuit population compared to the Danes population was attributed to the high intake of PUFA by the Inuit population. As a result, multiple studies have been conducted on the effect of fish (high in PUFA) consumption on cardiovascular mortality, including sudden death, with inconsistent results. The aim of this review is to evaluate the available evidences for and against the use of fish oil supplement on the prevention of cardiovascular events in patients with and without previous cardiovascular diseases.

Methods

The association between fish oil and coronary heart disease and the association between fish oil and ventricular arrhythmias was investigated by conducting a systemic review of studies using PubMed. Numerous Medical Subject Headings (MeSH) were used for the search: fish oil, polyunsaturated-omega-fatty-acids OR PUFA, coronary heart disease OR CHD, ventricular arrhythmias, ventricular fibrillation OR VF, ventricular tachycardia. Using the above search criteria we did a manual search of the references to find additional studies of interest. Our study was conducted in concordance with the Preferred Reporting of Observational Studies in Epidemiology (PRISMA) and the Observational Studies in Epidemiology (STROBE) statements.[8,9] Our systemic review included most of the human studies on the association between fish oil and coronary heart disease (CHD) and the association between fish oil and ventricular arrhythmias.

Results

Whelton et al conducted meta-analysis of 15 observational studies to determine if fish consumption is associated with lower fatal and total CHD. Fish consumption versus little to no fish consumption was associated with a relative risk of 0.83 (95% confidence interval 0.76-0.90; $P<$ 0.005) for fatal CHD and a relative risk of 0.86 (95% confidence interval 0.81-0.92; $P < 0.005$) for total CHD.[10] Meta-analysis by He et al showed progressively increasing reduction in CHD mortality with an increase in fish consumption. In this meta-analysis the authors were able to show that each 20 gm/day increase in fish intake was associated with a 7% lower risk of CHD mortality.[11]

Fish consumption and 30-year risk of fatal MI was assessed in a prospective observational study at the Chicago Western Electric Study. One thousand eight hundred twenty-two male participants between 40 and 55 years of age and free of cardiovascular disease at baseline were included in this study and followed for 31 years. The study found that there was an inverse relationship between fish consumption and death from CHD but no changes in the sudden cardiac death.[12]

The association between fish consumption and incidence of sudden cardiac death was done as a prospective cohort study of 20,551 US male physicians 40-84 years of age without any history of MI, cerebrovascular disease, and cancer at baseline. The study showed that consumption of fish at least once per week may reduce the risk of sudden cardiac death in men by 52% with a relative risk of sudden death of 0.48 (95% confidence interval 0.24-0.96; $P = 0.040$).[13] The GISSI trial also confirmed that supplementation with 1 gm daily of n-3 PUFA was associated with a clinically important and statistically significant reduction in death, nonfatal MI, and stroke in patients with a recent ($<$ or $= 3$ months) MI. Although the study was not specifically designed to analyze sudden death, much of the benefit was driven by this outcome.[14]

Contradictory results have been observed in studies on the effect of increased PUFA intake on ventricular arrhythmia. Fish oil has been associated with reduced ventricular arrhythmias, slower heart rate, and increased heart rate variability.[15-17] In contrast, Billman et al assessed the susceptibility to ventricular fibrillation (VF) using a 2-minute left circumflex artery occlusion during the last minute of an exercise test in 76 dogs with healed MI. The result showed that dietary n-3 PUFAs did not prevent ischemia-induced VF and actually increased arrhythmia susceptibility in both noninfarcted and low-risk post-MI dogs despite an increase in cardiac tissue n-3 PUFA content.[18]

A randomized controlled factorial trial by Burr et al has shown there was an excess sudden cardiac death among those who were supplied with fish oil capsule.[19,20] Another study was conducted by Jenkins et al to confirm PUFA's role in the prevention of sudden cardiac death. In this study, patients with an implantable cardioverter defibrillator (ICD) and a recent episode of sustained ventricular tachycardia and/or VF were randomly assigned to a PUFA or placebo group. During a median follow-up period of 718 days, in patients with a recent episode of sustained ventricular arrhythmias with an ICD, PUFA treatment did not reduce the risk of recurrence and it may even have been proarrhythmic in some patients.[21] Furthermore, in a subsequent meta-analysis of >500 patients by Jenkins et al, PUFA supplementation in patients with ICD did not show any overall effect of fish oil on the relative risk of ICD discharge with significant heterogeneity between the trials.[21]

Conclusion

Despite the increased use of fish oil supplement for both primary and secondary prevention of cardiovascular mortality and morbidity the available evidence of consistent benefit, particularly in preventing ventricular arrythmia related morbidity and mortality is conflicting. Further randomized controlled trials with adequate power need to be done to clearly establish the risk and benefit of PUFA supplementation in a population at a different level of cardiovascular disease risk.

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