Preventive Medicine

Potential Effects of Omega-3 Fatty Acid Supplements in the Prevention of Type 2 Diabetes: A Critical Appraisal of Data from Randomized Clinical Trials

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Abstract

Emerging evidence has suggested favorable effects of marine omega-3 fatty acids on glucose homeostasis, lipid metabolism, endothelial function, and chronic inflammation, which could contribute individually or synergistically to the development of type 2 diabetes (T2D). With increasing prevalence of use of fish oil supplements and increasing fortification of the food supply with marine omega-3 fatty acids in the general population, it will be critically important to assess the overall balance of benefits and risks of omega-3 fatty acid supplements on glucose tolerance and diabetes. This article aims to summarize the evidence from available randomized clinical trials on the potential effects of fish oil and/or omega-3 fatty acid supplements among both nondiabetic and diabetic participants. Overall, the evidence for the beneficial or deleterious effects of fish oil supplements on insulin sensitivity has been inconsistent, with limited randomized trial data involving small trials of short duration. However, dietary recommendation of taking omega-3 fatty acids for prevention of T2D or diabetic complications may ultimately only be resolvable by definitive data from future large-scale clinical trials that include T2D as a primary outcome in a general population. *[N A J Med Sci. 2010;3(3):140-145.]*

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Introduction

Type 2 diabetes (T2D) is considered "the epidemic of the 21st century", affecting approximately 24 million individuals in the U.S. alone, or nearly 8% of the U.S. population[1] and more than 170 million individuals worldwide.[2] Overall, it is estimated that the prevalence of diabetes will increase by 42% among adults living in developed countries and by 170% among adults in developing countries by 2025.[3, 4] Given the rising global burden of T2D and its devastating complications, there is a great urgency to develop effective strategies for curbing the epidemic by prevention and early treatment. Some dietary supplements have been advocated as an attractive option for preventing T2D because of their relative safety and affordability and several studies have suggested favorable effects of marine omega-3 fatty acids on glucose homeostasis.[5-7]

The omega-3 (ω-3) fatty acids are types of polyunsaturated fatty acids (PUFAs) with their first double bond between the 3rd and 4th carbon atoms. Two longer chain omega-3 fatty acids, eicosapentaenoic acid (EPA; 25:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3), are abundant in fish, shellfish, and sea mammals or fish oils and scarce or absent in land animals and plants. Alpha-linolenic acid (ALA, 18:3 n-3), a shorter chain omega-3 fatty acid, can be converted to longer-chain omega-3 fatty acids in the body; however, the rate of conversion by humans of ALA to EPA or DHA is very low, ranging from 0.2% to 15%.[8] PUFAs of the omega-3 series, primarily EPA and DHA, inhibit platelet aggregation, reduce blood pressure and endothelial activation, and have anti-inflammatory and antiarrhythmic properties.[7, 8] High intakes of fish or omega-3 fatty acids have been associated with a lower incidence of coronary heart disease and death. Emerging though limited data also suggested a link between omega-3 fatty acids and risk of T2D.

Omega-3 Fatty Acids and Pre-Diabetic Insulin Action and Pancreatic β-Cell Function

Dietary fat plays an important role in the induction of insulin resistance through two hypothesized mechanisms. First, a high percentage of fat in the diet may promote weight gain and adiposity to influence insulin resistance. Experimental studies conducted in rodent models have demonstrated that both the amount and the type of fatty acids ingested alter

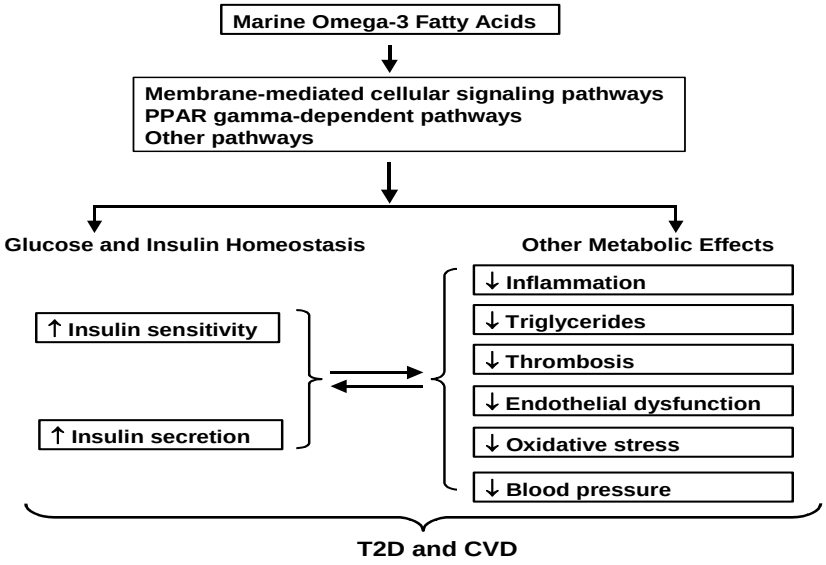

Figure 1. Mechanisms by which marine omega-3 fatty acids may affect T2D risk.

insulin sensitivity in target tissues (i.e., muscle, adipose tissue, and liver) and are associated with glucose intolerance and obesity.[9, 10] Second, higher total fat intake may directly affect insulin resistance, independent of obesity. Animal studies have shown that a high-fat diet enriched with omega-3 fatty acids prevents insulin resistance in muscle.[11] Long-chain polyunsaturated fatty acid, especially omega-3 fatty acid from fish, may play a role in glucose homeostasis, insulin action in peripheral tissues, and pancreatic insulin secretion. Although the exact mechanisms are not well understood, the effects of omega-3 fatty acids on glucose metabolism could be partly mediated via alteration of both the phospholipid and protein components of cell membranes[12] and regulation of peroxisome proliferator-activated receptor (PPAR)γ-dependent pathway (**Figure 1**). These changes in membrane phospholipid composition and membrane protein acylation may alter structure and fluidity of cell membranes and thereby could impact membrane-mediated processes such as insulin transduction signals, endocytosis, transcytosis, and cholesterol trafficking.[12] Moreover, omega-3 fatty acids and their metabolites are natural ligands for PPARs, particularly PPARγ.[13] PPARγ is a transcription factor that controls fat metabolism by regulating genes involved in lipogenesis, insulin sensitization, and adipocyte differentiation.[14] In addition, available evidence suggests that dietary omega-3 fatty acids may influence β-cell function through improvement of inflammatory status, endothelial function, and oxidative stress.[7,8,15-20]

Omega-3 fatty acid supplementation in animals and humans results in substantial increases in plasma and tissue EPA and DHA.[21-23] However, the evidence for the effects of fish oil supplements and insulin sensitivity in non-diabetic individuals remains inconclusive due to limited randomized data. In six randomized trials of non-diabetic participants (10-78 participants in each trial with trial duration from 4 to 24 weeks), omega-3 supplements (EPA+DHA, 2.5-4g/d) did not have any significant effect on insulin resistance or insulin sensitivity in healthy volunteers,[24] or persons with moderate hypertriglycerolemia,[25-27] hypertension,[28] or impaired glucose tolerance.[29] Three of six randomized clinical trials of fish oil provided an accurate assessment of insulin sensitivity and/or secretion using a hyperinsulinemic-euglycemic clamp and an oral glucose tolerance test. Overall, there was no evidence that fish oil caused any differences in fasting glucose, insulin, C-peptide levels, and post-challenge glucose and insulin response in the areas under the curves among obese patients with IGT (n=8),[29] non-diabetic patients with moderate hypertriglyceridemia undergoing coronary artery bypass grafting (n=57),[25] or persons with untreated hypertension.[28] Similarly, the evidence from diabetic patients has also been inconsistent and did not support the hypothesis that marine omega-3 fatty acids have a direct effect on improving insulin sensitivity among patients with T2D.[30-33]

Omega-3 Fatty Acids and Other Pre-Diabetic Metabolic Abnormalities

Numerous clinical and animal studies have shown effects of omega-3 fatty acids on insulin action, hypertension, dyslipidemia, systemic inflammation, oxidative stress, and endothelial dysfunction, as summarized in Figure 1.[7] Such favorable metabolic effects have led to the hypothesis that increased dietary intake or supplementation of omega-3 fatty acids lower the risk of T2D through its pleiotropic effects on many pre-diabetic risk factors.

First, fish oil supplements have been reported to improve insulin sensitivity and possibly β-cell function. Second,

dietary n-3 PUFA may also be related to lipid metabolism independent of its effects on insulin sensitivity. The triglyceride-lowering effect by omega-3 fatty acid supplements in nondiabetic individuals, diabetic patients, and patients with hyperlipidemia and cardiovascular disease has been well documented by randomized clinical trials.[34] Third, omega-3 fatty acids may have a modest antihypertensive effect. A recent meta-analysis of 8 clinical trials with pre- and post-intervention blood pressure (BP) on 747 participants showed that omega-3 fatty acid supplementation led to a nonsignificant reduction in systolic BP (-0.78 mmHg, 95% CI, -2.74 to 1.19, P=0.44) and diastolic BP (-0.79 mmHg, 95% CI, -1.96 to 0.37, P=0.18).[35,36] Of note, fish oil supplement formulation and dosage varied across individual trials and these differences might have contributed to differential results and led to difficulties in estimating the true effect on BP by omega-3 fatty acids. Fourth, there is some evidence that dietary omega-3 fatty acids may reverse adverse metabolic actions of visceral fat by reducing fat mass[37-39] or regulating adipose tissue function.[40-42] In particular, emerging evidence suggests that omega-3 fatty acids (EPA and DHA) serve as PPAR-γ ligands, leading to PPAR-γ activation and subsequent stimulation of adiponectin secretion.[41-44] As an adipose-derived cytokine, adiponectin has insulin-sensitizing, antiatherogenic, and anti-inflammatory properties.[45,46] Several intervention studies have considered the effects of omega-3 fatty acid supplementation on body weight. The beneficial effects of omega-3 fatty acid supplementation to reduce measures of adiposity have been observed in lean,[39] overweight,[47,48] and obese[49] individuals. However, most trials have used different control diets and administered only a relatively short-term dietary change, the long-term effect on weight loss by omega-3 fatty acid supplementation remains unclear. Finally, clinical data suggest that high intake of omega-3 fatty acids may have beneficial effects on oxidative stress, endothelial dysfunction,[50] coagulation, and platelet aggregation.[51,52] These metabolic abnormalities are not currently included in the conventional diagnostic criteria for the metabolic syndrome, but they coexist with insulin resistance in liver, skeletal muscle, and vascular endothelium and may contribute to T2D to different extents. The metabolic syndrome classically refers to a constellation of 3 or more metabolic abnormalities: abdominal obesity, high triglyceride levels, low HDL cholesterol levels, high blood pressure, and glucose intolerance.[53,54] Regardless of diverse definitions used for the metabolic syndrome, there is an emerging consensus that the metabolic syndrome (or insulin resistance syndrome) reflects the cluster of many correlated metabolic components contributing to the underlying pathophysiologic mechanisms of both T2D and atherosclerotic cardiovascular disease. Taken together, the beneficial effects of omega-3 fatty acids on a panel of metabolic abnormalities could contribute individually or synergistically to lowering the risk of T2D.

Table 1. Meta-analysis of randomized clinical trial data on the glycemic effects of omega-3 fatty acid (EPA/DHA) supplementation among patients with and without T2D.

Authors, Year	Trial	Subjects	Duration	EPA/DHA (g/d)	Fasting glucose, mmol/L	HbA1c, %
Friedberg, et al. 1998[60]	15	266 (T2D)	2-36 wk	1.34-5.4/0.20-3.0	0.43 (0.00, 0.87)	0.14 (-0.41, 0.68)
Montori, et al. 2000[33]	18	823 (T2D)	2-24 wk	1.08-5.20/0.3-4.8	0.26 (-0.08, 0.60)	0.15 (-0.08, 0.37)
Balk, et al. 2006[59]	21	578-1472 (T2D and non-T2D)	4-52 wk	0.6-4.6	0.17 (-0.01, 0.33)	0.10 (-0.01, 0.20)
Hartweg et al. 2009[31-32]	21	1030-1409 (T2D)	2-36 wk	0.52-1.8/0.48-3.0	0.09 (-0.31, 0.12)	-0.01 (-0.03, 0.01)

Omega-3 Fatty Acid Supplements and Diabetes-Related Phenotypes

Four decades ago, epidemiologists observed a low prevalence of impaired glucose tolerance and T2D among Alaskan natives, Greenland Eskimos and other Arctic and subarctic natives who consumed a large amount of fish compared with Danes and U.S. residents.[55-58] Based on these ecological and cross-sectional data, it has been hypothesized that increased intake of fish rich in omega-3 fatty acids may help delay or prevent the development of T2D.

However, the evidence for the effects of fish oil supplements and insulin sensitivity in non-diabetic individuals remains inconclusive due to limited randomized data. Similarly, the evidence from diabetic patients has also been inconsistent and did not support the hypothesis that marine omega-3 fatty acids have a direct effect on improving insulin sensitivity among patients with T2D.[30-33] There were four meta-analyses of randomized trials of fish oil supplements on glycemic biomarkers in which 15 or 21 randomized trials were included with trial durations of 2 to 52 weeks.[33,35,59,60] Of 4 meta-analyses, three studies have included randomized trials of T2D patients only (**Table 1**). In the latest updated one,[35] of 21 trials with measurement of HbA1c levels, omega-3 supplementation was associated with a modest but non-significant reduction in HbA1c (the pooled weighted mean difference=-0.01%, 95% CI, -0.03 to 0.01). Compared with

controls, omega-3 supplementation was not associated with a significant change in fasting glucose and insulin levels. In four trials evaluating change in C-peptide levels, a measure of insulin secretion, omega-3 supplementation seemed to increase C-peptide levels slightly and non-significantly (the pooled weighted mean difference=0.08 mmol/L, 95% CI, -0.08 to 0.24).[35] Given the small trials with short durations available, it is possible that a small-to-moderate effect in long-term glycemic control, as reflected by HbA1c levels, would be detectable in future large trials with longer duration. Supplement formulation and dosage also varied across previous trials. These differences may have contributed to differential results. Future long-term trials of sufficient duration are required to establish conclusively the role of omega-3 fatty acid supplementation in glycemic controls.

Although several early randomized trials using high fish oil consumption (≥10 g fish oil per day) reported possible adverse effects on glycemic control and insulin action in patients with T2D,[61-66] more recent data suggest that fish oil supplementation at relatively lower doses (1 to 2 g/day) may not have a detrimental effect on glycemic status.[33,35,59] Except for one early meta-analysis of 15 trials,[60] three updated meta-analyses including more trial data appear to indicate no significant impact on glycemic control among diabetic patients (**Table 1**).[33,35,59] Results from other randomized trials of non-diabetic individuals are consistent with these findings in diabetic patients[24-26,28,29,67] and do not support the hypothesis that marine omega-3 fatty acids have detrimental effects on elevating fasting glucose or glucose intolerance. Two largest meta-analyses showed no evidence for the effects of fish oil supplementation on either HbA1c or fasting glucose levels.[35,59]

Several small and short-term randomized trials among patients with T2D conducted to evaluate the effect of omega-3 supplementation on lipoprotein profiles have yielded inconsistent results. In an updated meta-analysis,[31] a total of 1,075 patients with T2D were enrolled in 23 randomized controlled trials comparing omega-3 fatty acids with placebo (median 3 g/day, range 0.9-10 g/day). Most individual trials were of short duration ranging from 2 to 24 weeks (mean: 8.9 weeks). There were no adverse effects reported for different doses (0.9-10 g/day) and forms of omega-3 supplements (dietary or non-dietary). Overall, omega-3 supplementation appeared to lower triglyceride levels by 25% (mean difference, -0.45 mmol/L; 95% CI, -0.58 to –0.32 mmol/L), VLDL-triglyceride levels by 39.7% (-0.44 mmol/L; 95% CI, -0.83 to –0.05 mmol/L), and VLDL-cholesterol by 36% (-0.07 mmol/L; 95% CI, -0.13 to 0.00). Omega-3 supplementation did not lead to significant changes in LDL-cholesterol, total or HDL cholesterol, and other lipid and lipoprotein levels.[31]

Overall, these experimental data are helpful not only to provide direct evidence for possible cardioprotective effects or anti-diabetic benefits of omega-3 fatty acid supplementation but also to evaluate potential risks as well as optimal formulation and dosage. However, many sources of heterogeneity may have contributed to the inconsistency of results including small sample size, incomplete randomization, the lack of blinding in design, variable duration of follow-up, high rates of noncompliance, and differences in treatment protocols, fish oil formulation and dose, and study populations. To the best of our knowledge, no previous randomized trials have directly assessed the efficacy of fish oil supplements in the primary prevention of T2D. Hence, the balance of benefits and risks associated with long-term fish oil supplementation to health status in general and to the prevention of T2D in particular are warranted.

Optimal Dose of Omega-3 Fatty Acid Supplements

There has been much controversial over the dose of fish oil supplements. The optimal dose of EPA/DHA in a single capsule is believed to provide the best balance of efficacy and safety. On the basis of the observational and randomized trial data, health authorities recommend 400 mg to 1 g/d of EPA and DHA combined for cardioprotection.[68,69] However, the typical U.S. adult consumes only 100-200 mg/d of EPA+DHA.[68] Many people find it difficult to eat two fish meals per week, let alone ~1g/d of EPA+DHA, which translates to more than one fish meal daily, and concerns have been raised about environmental contamination of the fish supply. Thus, fish oil supplements may be a preferable way to achieve compliance. Because the optimal ratio of EPA to DHA is unknown,[17,70] in general, a 1:1 ratio of EPA to DHA was chosen. Health risks associated with fish oil are believed to be minimal. The FDA has concluded that marine omega-3 fatty acid doses of up to 3 g/d are "Generally Recognized as Safe".[71] Although omega-3 fatty acids have potential antithrombotic effects, systematic reviews of data from small, short-term trials suggest that omega-3 fatty acid supplements do not increase the risk of clinically significant bleeding at doses of up to 4 g/d, even in combination with anticoagulant medications such as aspirin or warfarin.[72,73]

Summary

Pathogenesis of T2D is a multi-factorial process that generally involves a complex interaction among multiple etiologic factors. Despite much progress in biomedical science, T2D continues to be a leading cause of death and disability for millions of Americans. While observational data in humans and experimental animal studies suggest that omega-3 fatty acids may help prevent T2D through their beneficial pleiotropic effects on metabolic phenotypes, data from randomized clinical trial are limited. The evidence for the deleterious effects of fish oil supplements on insulin sensitivity has been inconsistent, with limited randomized trial data involving small trials of short duration. Despite the potential significance of omega-3 fatty acid supplements for T2D prevention, it is surprising that few prospective studies have directly examined their use in this application. The lack of randomized trial data precludes recommendations for the general population. With increasing prevalence of use of fish oil supplements and increasing fortification of the food supply with omega-3 fatty acids in the general population, future large-scale and well-designed randomized clinical trial will provide definitive data on both benefits and potential

adverse effects of omega-3 fatty acids in the prevention of T2D. Unless future studies provide updated knowledge, for diabetes prevention with omega-3 supplementation, it may be wise to follow the American Heart Association's recommendation for fish consumption since cardiovascular disease and diabetes share many risk factors.

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