

Effect of Omega-3 Polyunsaturated Fatty Acids and Vitamin D on Cardiovascular Diseases

Ibrahim Marai MD and Samia Massalha MD

Department of Cardiology, Rambam Health Care Campus, affiliated to Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

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Numerous epidemiological and observational studies and meta-analyses have investigated the effect of omega-3 polyunsaturated fatty acids and vitamin D on cardiovascular disease outcomes. This review summarizes the clinical evidence of the benefit of PUFA in CVD [Table 1], and the relation of vitamin D status to CVD [Table 2].

PUFA = polyunsaturated fatty acids
CVD = cardiovascular disease

Table 1. Effect of omega-3 on cardiovascular diseases in different studies

	Ref	Study group	Results
Risk factors	[3]	Human studies, hyperlipidemia	LDL-C tendency to rise by 5–10%, HDL-C rise by 1–3%, triacylglycerol decrease by 25–30%
	[4]	Meta-regression analysis of randomized trials	High intake of fish oil may lower blood pressure
	[5]	Diabetes	No change in glycemic control
Ischemic heart disease	[6,7]	Patients after MI	Reduction in total and cardiovascular mortality
	[9]	Post-MI	Alpha-linolenic acid associated with lower risk of MI
	[10]	Angina pectoris	Increased risk of cardiac death
	[11,12]	Acute MI	No clinical benefit
	[13-15]	Patients referred for coronary angiography	Decrease in restenosis rate, increase in restenosis rate
Arrhythmias	[17]	Meta-analysis of three ICD trials	No protective effect on the incidence of ventricular arrhythmia
	[18,19]	Patients after cardioversion [18] or ablation [19] for AF	Reduction in AF recurrence
	[21]	Patients with paroxysmal AF	No reduction in recurrent AF
	[22,23]	Patients who underwent CABG	Reduced postoperative AF
	[24,25]	Patients who underwent cardiac surgery	No reduction in postoperative AF
Heart failure	[26]	Heart failure, NYHA II-IV	Small advantage in terms of mortality and hospitalization
	[28,29]	Subjects free from heart failure	No major role in the prevention of heart failure

MI = myocardial infarction, ICD = implanted cardioverter defibrillators, AF = atrial fibrillation

OMEGA-3 PUFA

Most of the evidence of the benefits of omega-3 PUFA was obtained for long-chain fatty acids, eicosapentaenoic acid and docosahexaenoic acid, the active components of fish oils [1]. Humans get omega-3 PUFA from fish oils. The original source of the omega-3 found in fish oils is marine microorganisms.

The current American Heart Association dietary guidelines recommend combined EPA and DHA at a dose of approximately 1000 mg/day for secondary prevention of coronary heart disease and consumption of two oily fish meals per week (equivalent to about 500 mg/day of combined EPA and DHA) for primary prevention [2]. In patients with hypertriglyceridemia, moderate to high doses of PUFA (2–4 g/day) are required in addition to other lipid-lowering treatment.

EPA = eicosapentaenoic acid
DHA = docosahexaenoic acid

Table 2. Effect of vitamin D on cardiovascular disease in different studies

Ref	Study group	Result
[30]	Cardiomyocyte-specific VDR knockout mice	Vitamin D deficiency-induced hypertrophy of myocytes
[32]	Animal models	Excess of vitamin D associated with the de novo production of bone in the vessel wall
[34]	German population	Higher vitamin D levels associated with decreased risk of IHD
[35]	Patients referred for coronary angiography	Vitamin D insufficiency associated with cardiovascular morbidity and mortality
[36]	Population with low exposure to sun	No association between vitamin D deficiency and CVD
[37]	Population with high exposure to sun	Decreased incidence of metabolic syndrome among patients with normal vitamin D levels
[38]	Patients with metabolic syndrome	Optimal vitamin D levels lowered mortality
[40]	Men who participated in the Health Professionals Follow-up Study	Vitamin D deficiency associated with increased risk of developing MI

VDR = vitamin D receptor, IHD = ischemic heart disease, CVD = cardiovascular disease, MI = myocardial infarction

PUFA FOR TREATMENT OF RISK FACTORS

PUFA reduce hepatic synthesis of triglycerides and increase hepatic fatty acid beta-oxidation. In a review of studies on the effect of PUFA on serum lipoproteins it was noted that total cholesterol is not materially affected by PUFA consumption, low density lipoprotein-cholesterol concentrations tend to rise by 5%–10% and high density lipoprotein-cholesterol by 1–3%, and serum triacylglycerol concentrations decrease by 25–30% [3].

The antihypertensive effects of PUFA have been analyzed in series of trials and meta-analyses. In a meta-regression analysis of randomized trials, Geleijnse et al. [4] found that high intake of fish oil may lower blood pressure, especially in older and hypertensive subjects. The antihypertensive effect of lower doses of fish oil (< 0.5 g/day), however, remains to be established. Most studies in the area of glucose tolerance suggest that there is no significant improvement or change in glycemic control due to PUFA [5].

PUFA FOR TREATMENT OF ISCHEMIC HEART DISEASE

Burr and collaborators [6] found in a randomized controlled trial of men who had recovered from myocardial infarction that intake of fatty fish caused a 29% reduction in 2 year all-cause mortality compared with those not so advised.

In another randomized trial, 11,324 patients surviving recent myocardial infarction were randomly assigned supplements of PUFA (1 g daily), vitamin E, both, or none for 3.5 years [7]. Treatment with PUFA, but not vitamin E, caused a 15% reduction in the primary endpoint, including a 20% and 30% reduction in total and cardiovascular mortality respectively [7]. Further analysis showed that this endpoint reduction was driven by a highly significant reduction in sudden death.

In another trial (of primary and secondary prevention), 18,645 patients with hypercholesterolemia were randomly assigned to receive either 1800 mg of EPA daily with statin, or statin only, with a 5 year follow-up [8]. Patients randomized to EPA had a 19% reduction in major cardiovascular events. Serum LDL-cholesterol was not a significant factor in reduction of risk for major coronary events [8].

Intake of long chain omega-3 fatty acids found in fish is low in many countries worldwide. Alpha-linolenic acid, an essential omega-3 fatty acid found in vegetable cooking oils such as soybean and canola oils and other products of plant origin, could be a viable cardioprotective alternative to these fatty acids in these countries. Campos et al. [9], investigating the effect of consumption of vegetable oils rich in ALA on post-myocardial infarction patients, found that greater ALA (assessed either in adipose or by questionnaire) was associated with lower risk of myocardial infarction in post-myocardial infarction patients.

LDL = low density lipoprotein
ALA = alpha-linolenic acid

In contrast, other studies showed a negative effect of PUFA in coronary heart disease. A randomized controlled factorial trial showed that the risk of cardiac death was higher among men under 70 years of age with angina who were advised to take two portions of oily fish each week or to take three fish oil capsules daily than among those not so advised [10]. The excess risk was mostly present in the subgroup given fish oil capsules. In another trial, there was no clinical benefit of a high dose concentrate of omega-3 fatty acids over 12–24 months compared with corn oil despite a favorable effect on serum lipids among patients with acute myocardial infarction [11]. Low dose supplementation with EPA-DHA or ALA did not significantly reduce the rate of major cardiovascular events among 4837 patients (age 60–80 years) who had had a myocardial infarction and who were receiving state-of-the-art antihypertensive, antithrombotic and lipid-modifying therapy in a multicenter double-blind placebo-controlled trial [12].

Studies investigating the efficacy of PUFA on restenosis after coronary intervention are conflicting. In a double-blind randomized controlled trial 205 patients undergoing a first percutaneous transluminal coronary angioplasty received either fish oil (2.7 g/day EPA, 1.8 g/day DHA) or olive oil [13]. The treatment was started 3 weeks before PTCA and continued for 6 months thereafter. At 6 months after PTCA, patients underwent a control angiography. Restenosis occurred less often in the fish oil group (22.0–35.6%) than in the control group (40.0–53.3%), indicating a protective effect of fish oil supplements on restenosis.

In another double-blind placebo-controlled study, patients were randomized for omega-3 fatty acids (high dose of EPA acid and DHA started 1 month before PTCA and given for 1 month thereafter, then continued at half-dose for 6 months) versus an olive oil placebo [14]. With a long treatment before PTCA, omega-3 fatty acids produced a small but significant decrease in the restenosis rate compared with placebo at 6 months angiographic follow-up.

In contrast, in a randomized double-blind trial conducted in 204 patients the incidence of angiographic restenosis was higher (34%) in the fish oil group (6 g/day of omega-3 fatty acids, beginning 5.4 days before PTCA and continuing for 6 months) compared to the control group (23%) [15].

THE EFFECT OF PUFA ON ARRHYTHMIAS

Several randomized trials have shown that PUFA improve sympathovagal balance and improve autonomic function. Current research suggests that PUFA prevent arrhythmia via their ability to inhibit fast, voltage-dependent sodium channels and l-type calcium channels. Clinical trials have demonstrated different effects of PUFA on arrhythmic events.

PTCA = percutaneous transluminal coronary angioplasty

It was reported that PUFA can prevent sudden death [1,7], but many studies did not support this finding. A randomized placebo-controlled double-blind multicenter trial (called OMEGA) tested the effects of PUFA (1 g/day for 1 year) on the rate of sudden cardiac death in survivors of acute myocardial infarction, if given in addition to current guideline-adjusted treatment starting 3–14 days after acute myocardial infarction [16]. This trial showed no benefit of PUFA on any of the primary or secondary endpoints in these patients [16]. Meta-analysis of three implanted cardioverter defibrillator trials showed no convincing protective effect of omega-3 PUFA on the incidence of recurrent ventricular arrhythmia among patients with this device [17].

An anti-arrhythmic effect of PUFA is pronounced in atrial fibrillation. In an open-label randomized study of 178 patients with persistent AF > 1 month duration, participants were assigned to a control group or the omega-3 group (6 g/day fish oil, combined EPA and DHA) and underwent cardioversion 1 month later [18]. At 90 days, omega-3 PUFA intake was associated with a significant reduction in AF recurrence with or without concurrent anti-arrhythmic drugs. Patel and co-authors [19] reported in a nested case-controlled analysis that patients with pulmonary vein antrum isolation treated with PUFA had lower incidences of early AF recurrence and procedural failure compared to an untreated population.

In contrast, in the Rotterdam study (a prospective cohort study), intakes of EPA and DHA and the consumption of fish were not associated with the onset of AF [20]. In addition, treatment with omega-3 PUFA for 24 weeks did not reduce recurrent AF over 6 months among participants with paroxysmal AF compared to placebo [21].

Many studies were undertaken to evaluate the role of PUFA in prevention of post-cardiac surgery AF. In a prospective randomized study, PUFA administration of 2 g/day for at least 5 days before elective coronary artery bypass graft and until the day of discharge from hospital reduced the incidence of postoperative AF and was associated with a shorter hospital stay [22]. Perioperative intravenous infusion of PUFA reduced the incidence of AF after CABG and led to a shorter stay in the intensive care unit and in hospital [23].

In contrast, omega-3 PUFA did not reduce the risk of postoperative AF among patients undergoing CABG surgery who were randomly assigned to receive 2 g/day omega-3 PUFA compared to placebo for at least 5 days before surgery [24]. In another randomized study, 200 patients were randomized to receive fish oil (4.6 g/day omega-3 fatty acids) or a control oil starting 3 weeks before cardiac surgery [25]. Supplementation with dietary fish oil did not result in a significant decrease in the incidence of postsurgical AF. However, there was a significant decrease in time spent in the intensive care unit.

BENEFIT IN HEART FAILURE

In GISSI-HF, patients with chronic heart failure of New York Heart Association class II-IV, irrespective of cause and left ventricular ejection fraction, were randomly assigned to omega-3 PUFA 1 g daily (n=3494) or placebo (n=3481) [26]. Treatment with omega-3 PUFA provided a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular reasons. Yamagishi et al. [27] reported an inverse association between fish and PUFA consumption and cardiovascular mortality, especially for heart failure, in a prospective study consisting of 57,972 Japanese men and women followed for 12.7 years.

In contrast, Dijkstra et al. [28] examined EPA plus DHA and fish intake in relation to incident heart failure in the population-based Rotterdam Study. The analysis comprised 5299 subjects (41% men, age approximately 68 years) free from heart failure for whom dietary data were available. Their findings do not support a major role for fish intake in the prevention of heart failure. In addition, Belin and team [29] found no significant associations between EPA and DHA, ALA or trans-fatty acid intake, and incident HF.

In summary, overall, the findings indicate that the consumption of omega-3 PUFA may reduce cardiovascular morbidity and mortality in populations with and without CVD. However, studies have not shown consistency in the effect of omega-3 PUFA on CVD and risk factors. Ethnicity and culture are factors that can account for some of this variation. In addition, different forms and doses of PUFA intake, and different relative ratio of EPA and DHA used in the studies, can also account for inconsistent results. Further studies are needed to determine the optimal dosage and the relative ratio of DHA and EPA omega-3 PUFA for the primary and secondary prevention of cardiovascular diseases.

VITAMIN D

Vitamin D is a fat-soluble vitamin that exerts its physiological effects through attachment to its receptor, which is distributed in a wide variety of cell types in human and animal tissue. Several studies of human and animal cells indicated the presence of the VDR in most cells in the body including myocytes and vascular smooth muscle cells. Active vitamin D inhibits *in vitro* cell proliferation, induces differentiation and apoptosis, improves vascular compliance, decreases parathyroid hormone levels, improves glycemic control, and thus may have a role in cardiovascular diseases. Vitamin D also exerts anti-inflammatory effects, and its deficiency was suggested to be related to inflammatory and autoimmune diseases.

Vitamin D insufficiency is prevalent worldwide and it is estimated that one billion subjects have some kind of this insuf-

AF = atrial fibrillation
CABG = coronary artery bypass graft

VDR = vitamin D receptor

iciency. The cutoff level for vitamin D insufficiency varies in different studies but in general is 30 nmol/L (12 ng/ml). Despite the intensive and diverse research of vitamin D insufficiency and/or deficiency, its association with CVD is still controversial.

The cardiovascular involvement was found to range from hypertrophy and fibrosis to vascular involvement and ischemic heart diseases. A recent study [30] created cardiomyocyte-specific VDR knockout mice and showed that the induction of hypertrophy by the infusion of isoproterenol was more pronounced in these mice than in mice with intact VDR. The same study found little evidence of interstitial fibrosis in the cardiac-specific VDR knockout.

The vascular involvement was attributed to the effect of vitamin D insufficiency on the protein fetuin-A, a glycoprotein produced in the liver and believed to be a calcification inhibitor that captures calcium molecules in the vessel walls forming calcioprotein particles, preventing aggregation into insoluble mineral crystals and preventing further growth [31]. More recent studies suggested that excess of vitamin D is in fact associated with the *de novo* production of bone in the vessel wall, rather than precipitation of calcium into the vessel walls [32]. High dose dietary vitamin D reliably induces medial calcification; it is often used to generate animal models of vascular calcification. As a fat-soluble vitamin, dietary vitamin D may be carried by chylomicrons and lipoprotein particles, which are deposited into the artery wall where it may be converted to active form by 1- α -hydroxylase in vascular smooth muscle cells and in monocyte-macrophages [32]. This raises interesting questions about the potential of vitamin D to promote atherosclerotic calcification and cardiovascular risk. On the contrary, as shown by other publications, vitamin D and its derivatives suppress proliferation of vascular smooth muscle cells in culture and inhibit cholesterol sequestration in macrophages [33] – two steps that are linked to the progression of vascular lesions in atherosclerosis.

CLINICAL DATA

Prospective studies, such as the MONICA/KORA Augsburg Case-Cohort Study [34] in a German population, suggested that higher vitamin D levels are associated with decreased risk of coronary heart disease. This effect is more pronounced in women than in men [34]. Low levels of 25-hydroxy vitamin D and 1,25-dihydroxy vitamin D are associated with prevalent myocardial dysfunction, deaths due to heart failure, and sudden cardiac death [35].

It is logical to think that if this association was true, cardiovascular disease would be more pronounced in populations less exposed to ultraviolet B sunlight and vice versa. Interestingly, two studies from two extreme regions in terms of sun exposure showed non-conclusive results. The MIDSPAN study, a prospective study conducted in Scotland (low exposure to sunlight) comparing a cohort with vitamin deficiency to a normal level of vitamin D, showed no asso-

ciation between vitamin D deficiency and cardiovascular diseases, although there was an association with all-cause mortality [36]. On the other hand, a prospective Saudi study found a decreased incidence of metabolic syndrome (known risk factor for cardiovascular diseases and cardiovascular death) in a population with high exposure to sunlight [37].

Other similar studies such as the LURIC (Ludwigshafen Risk and Cardiovascular Health), a prospective cohort study designed to evaluate determinants of cardiovascular health, have also shown that optimal 25-hydroxy vitamin D levels substantially lowered all-cause and cardiovascular disease mortality in subjects with the metabolic syndrome [38]. The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) prospectively showed that lower 25-hydroxy vitamin D concentrations were associated with increased metabolic syndrome risk and higher waist circumference, serum triglycerides, fasting glucose, and insulin resistance at 5 years follow-up [39].

Further evaluation of a connection to coronary heart diseases was assessed by Giovannucci and colleagues [40], who found an association between serum 25-hydroxy vitamin D and risk of coronary disease among men who participated in the Health Professionals Follow-up Study. In this study, men with vitamin D deficiency (≤ 15 ng/ml or 37 nmol/L) were at significantly increased risk of developing myocardial infarction, compared to those with sufficient levels of vitamin D (≥ 30 ng/ml or 75 nmol/L).

From the above conflicting data – on both the cellular and the clinical level, both proved by laboratory data or prospective studies respectively – one concludes that there is a long way yet to go in researching this topic. We do know from pathophysiological studies and histology studies that vitamin D is involved in the de-differentiation of vascular smooth muscles into a synthetic phenotype that evolves into osteoblasts. On the other hand, we have evidence from studies showing that vitamin D is actually involved in the inhibitory pathway that includes fetuin-A, mentioned above.

As for the clinical scale and clinical research, the data are indeed conflicting and not conclusive. We are perplexed as to whether this contradiction might be derived from the upper level of vitamin D rather than the lower limit, meaning that excess of vitamin D levels might predispose to cardiovascular diseases, at least as much as vitamin D insufficiency might be associated with such pathologies. Thus, further studies are needed to answer this issue.

CONCLUSIONS

Omega-3 PUFA and vitamin D are widely taken by healthy people, patients with risk factors and patients with CVD. However, the available data do not support their efficacy among healthy subjects and patients with specific cardiac diseases. Thus, these supplements should not be used without evidence-based medicine.

Corresponding author:

Dr. I. Marai

Dept. of Cardiology, Rambam Health Care Campus, Haifa 31096, Israel

Phone: (972-4) 854-2180

Fax: +972-4-8542354

email: i_marai@rambam.health.gov.il

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