Application of polyunsaturated fatty acids in internal medicine: beyond the established cardiovascular effects

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Abstract

n-3 Polyunsaturated fatty acids (PUFAs) are organic acids, essential for mammals, whose deficiency is associated with different diseases. The American Heart Association recommends that all adults increase food-derived n-3 PUFA intake and also suggests that patients with documented coronary heart disease consume approximately 1 g of eicosapentaenoic acid and docosahexaenoic acid per day. However, recent evidence broadens their potential application to many other health disorders directly or indirectly associated with cardiovascular disease risk such as rheumatological diseases, mood depression, chronic kidney disease, chronic inflammatory lung diseases and others. These effects seem to be largely dependent on the dosages employed and on the characteristics of the selected patients. The cardiometabolic effects of PUFAs have been largely reviewed elsewhere, so the aim of our review is to point out the potential usefulness of such drugs with pleiotropic effects in the management of the actual typical aging patient, with co-morbidities and multidrug therapies.

Key words: polyunsaturated fatty acids, docosahexaenoic acid, eicosapentaenoic acid, internal medicine.

Introduction

Polyunsaturated fatty acids (PUFAs), organic acids that naturally contain more than one double bond in the aliphatic chain, are named according to the number (> 1), position, and configuration of such double bonds, which also largely determine their physical and biological properties. Polyunsaturated fatty acids are essential for mammals, which lack the enzyme to insert the double bond in the n-6 or n-3 position, and their deficiency is associated with various diseases [1]. While n-6 PUFAs are relatively abundant in a regular diet and there is no substantial evidence of their therapeutic potential when supplemented in the diet [2], n-3 PUFA supplementation is being studied as a potential treatment or preventive agent for numerous diseases (Table I). On the basis of currently available evidence, the American Heart Association (AHA) has recommended that all adults eat fish (particularly fatty fish) at least twice a week, as well as vegetables containing plant-derived n-3 fatty acids. The AHA also suggests that patients with documented coronary heart disease consume approximately 1 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (combined) per day, from oily fish or fish-oil capsules (after consultation with a physician). The AHA recommendations also state that EPA/DHA supplements may be useful in patients with severe hypertriglyceridemia

(> 500 mg of triglycerides per deciliter [5.6 mmol/l]), for whom effective doses are higher: 2 g to 4 g of EPA/DHA per day to lower triglyceride levels by 20-40% [3].

The cardiometabolic effects of PUFAs have been largely reviewed elsewhere [4], so the aim of our narrative review is to point out the potential usefulness of such drugs with pleiotropic effects in the management of the typical internal medicine patient, with polypathology and multidrug therapies. The literature search was based on PubMed references and cross-matched citations, giving a preference for data from recent randomized clinical trials and meta-analyses.

Prevention of arrhythmias

Arrhythmias are one of the leading causes of mortality after myocardial infarction. The antiarrhythmic effect of n-3 PUFAs after a myocardial infarction has been clearly demonstrated by some large trials such as the Diet and Reinfarction Trial (n = 2.033, relative risk of total mortality = 29%) [5] and by The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione Trial (n = 11324, RR of total mortality = 20%, RR of sudden death = 49%) [6]. Similar results have also been found in the large and more recent GISSI Heart Failure study, but mainly in patients with heart failure of ischemic origin [7].

Such results have not been confirmed by the large Alpha Omega trial carried out with lower dosage of EPA/DHA, in older patients who had a myocardial infarction a mean of 4 years before the beginning of the treatment [8]. This may suggest that the PUFA preventive activity against arrhythmias has a dosage threshold, is stronger when the treatment begins just after the event, and is probably more effective in younger patients. However, the outcome of the EPA-DHA supplementation in this study is difficult to interpret because the supplementation dose was small and its effects might have been obscured by the larger amount of ALA administered in half the groups in the comparison. In this instance, the factorial design of the study was inappropriate for the two non-independent study drugs tested. Furthermore, the study was underpowered to detect differences between each of the four study groups.

Studies in patients surviving malignant ventricular arrhythmias of different etiologies treated with an implantable cardioverter-defibrillator (ICD) have given conflicting results, even if suggesting a trend toward a protective effect [9]. However, it seems

Table I. Examples of diseases for which clinical evidence supports the use of n-3 PUFAs as possible therapeutic agents or is inconclusive

Variable	Clinical evidence	Inconclusive evidence
Cardiovascular diseases	• Post-infarct sudden death • Heart failure • Hypertension • Endothelial dysfunction/atherosclerosis • Prothrombotic syndromes	• Arrhythmias (dose-threshold) • Atrial fibrillation
Metabolic disorders	• Primary and secondary hypertriglyceridemias • Small dense LDL level	• Diabetes • LDL level • LDL oxidation
Chronic renal diseases	• IgA nephropathy • Diabetic renal disease	• Autosomal dominant polycystic kidney disease
Neurological diseases	• Multiple sclerosis • Some epilepsies • Stroke	• Cognitive decline • Alzheimer disease • Refractory epilepsy
Psychiatric diseases	• Depression • Psychoses	
Rheumatological and other immunological diseases	• Osteoporosis • Rheumatoid arthritis • Systemic lupus erythematosus • Psoriasis • Atopic eczema • Inflammatory bowel diseases	• Crohn's disease
Respiratory diseases	• Adult asthma • Cystic fibrosis	• Pediatric asthma
Eye diseases	• Macular degeneration • Dry eye	
Others		• La Peyronie's disease

that n-3 PUFAs are not effective in reducing atrial fibrillation recidivism after direct current electrical cardioversion [10].

Effects on chronic heart failure

Chronic heart failure is a highly prevalent disease in internal medicine departments. It has been supposed that n-3 PUFAs could have some protective effect against heart failure because of the effects on prevention of arrhythmias and the above listed metabolic and vascular effects. This observation has been confirmed in different trials. Supplementation with 2 g/day n-3 PUFAs has been associated with significant reduction of the serum N-terminal pro-brain natriuretic peptide level, a well-known markers of heart failure [11]. In a recent small but well-designed double-blind randomized clinical trial carried out on severe heart failure patients, it was observed that left ventricular ejection fraction increased with n-3 PUFA treatment in a dose-dependent manner in 3 months, with the best results obtained with dosage of 4 g/day [12]. However, in a subgroup analysis of the GISSI-HF trial it was observed that left ventricular ejection fraction increased with just 1 g/day n-3 PUFA by 8.1% at 1 year, 11.1% at 2 years, and 11.5% at 3 years vs. 6.3% at 1 year, 8.2% at 2 years, and 9.9% at 3 years in the placebo group (p = 0.0050) [13].

Therefore, some lines of evidence suggest that n-3 PUFAs could have a direct protective effect on the myocardium [14]. For instance, a recent randomized clinical trial carried out on patients affected by non-ischemic dilated cardiomyopathy with minimal symptoms demonstrated that 12 months of supplementation with 2 g/day of n-3 PUFAs was associated with a significant improvement of left ventricular ejection fraction, peak VO_2, exercise duration, mean New York Heart Association functional class, and hospitalization rates for heart failure [15].

Modulation of blood pressure levels

Systemic hypertension is a pandemic major independent cardiovascular risk factor, and the reduction by just a few mm Hg of systolic or diastolic blood pressure is associated with a significant reduction in the risk of developing a coronary or cerebrovascular disease [16]. Numerous randomized clinical trials have clearly demonstrated that n-3 PUFAs have an improving effect on endothelial function, especially in subjects at high risk of cardiovascular disease [17]. The antihypertensive effect of n-3 PUFAs has also been observed in patients at known increased cardiovascular risk such as those affected by chronic renal failure [18]. A meta-analysis of 36 randomized trials found a mean reduction in systolic blood pressure (SBP) of 2.1 mm Hg and in diastolic blood pressure (DBP) of 1.6 mm Hg [19], significantly inferior to that reported in some single trials [20]. The main reason for this low observed effect is that the meta-analysis included trials where low-dose or unpurified formulations were used, and where blood pressure reduction was not a main outcome of the study [21].

Effects on secondary dyslipidemias

It is well known that n-3 PUFAs have a dose-dependent lowering effect on serum triglycerides [22], whose role as cardiovascular disease risk factors has been recently reconsidered [23]. Other metabolic effects of n-3 PUFAs on lipid profile, related to serum triglycerides reduction, are a small increase of serum high-density lipoprotein (HDL) cholesterol, a significant reduction of post-prandial lipemia and a significant increase in the volume of atherogenic small, dense low-density lipoproteins (LDLs) [24]. Hypertriglyceridemia, low HDL-C, and small, dense LDL are the atherogenic lipid triad, characterizing the lipid pattern of metabolic syndrome, diabetic dyslipidemia and familial combined hyperlipidemia, all conditions associated with a very high cardiovascular disease risk [25]. However, n-3 PUFAs have no quantitative effect on the circulating LDL [26]. Because of their virtual lack of pharmacological interaction and high safety profile, they could have a specific application in the management of hypertriglyceridemia and related dyslipidemias secondary to pharmacological treatments or diseases associated with an adverse metabolic profile. A short list of these conditions is listed below. The use of n-3 PUFAs as therapeutic agents for hypertriglyceridemia in the context of global cardiovascular disease management has recently been evaluated as cost-effective [27].

Non-alcoholic steatohepatitis (NASH) is a highly prevalent metabolic disorder, characterized by fat infiltration of the liver cells, associated with an increase of cardiovascular disease risk and diabetes, and for which no specific care is currently available [28]. n-3 PUFA seems to efficiently improve the metabolic pattern and to reduce the liver fat content of NASH patients, both in adults [29] and in children [30].

Polycystic ovary syndrome (PCOS) is characterized by relative hyperandrogenism and by an adverse metabolic profile, simulating a metabolic syndrome, usually with hypertriglyceridemia, overweight and impaired fasting glucose. Supplementation with n-3 PUFAs improves the lipid pattern and androgenic profile in PCOS patients [31].

Chronic kidney disease (CKD) is also a very frequent condition in internal medicine practice. It is associated with premature cardiovascular disease and markedly disturbed lipid metabolism manifesting as elevated triglyceride concentrations,

reduced HDL cholesterol concentrations and a preponderance of small, dense LDL particles [32]. Beyond their known effects on dyslipidemias, n-3 PUFAs could reduce the oxidative stress biomarkers of CKD patients [33]. Moreover, some trials show that n-3 PUFAs delay the rate of loss of renal function in patients with IgA nephropathy [34], but also of diabetic nephropathy [35]. In particular, in IgA nephropathy, n-3 PUFAs potentiate the antiproteinuric effect of angiotensin receptor blockers [36]. Additionally, studies of omega-3 supplementation in dialysis patients describe salutary effects on triglyceride levels and dialysis access patency [37]. These effects are also probably dose-related.

Some drugs such as second generation antipsychotics [38] and highly active antiretroviral therapy (HAART) [39] are associated with an adverse lipid profile and overall with a phenotypic pattern leading to an increased cardiovascular disease risk. Moreover, they often have a high risk of pharmacological interaction with lipid-lowering drugs. In these patients, n-3 PUFAs could contribute to better control of the lipid profile and to a useful anti-inflammatory reaction [40].

In antipsychotic treated patients n-3 PUFAs have the potential to improve the lipid pattern and the drug-related arrhythmia risk [41], but also to reduce some psychosis related symptoms [42]. The n-3 PUFA supplementation in HIV patients treated with HAART is associated with a significant improvement in dyslipidemia and biomarkers of systemic inflammation level, without significant change in renal and liver enzymes [43].

The main limitation of the above listed effects is the lack of large clinical trials demonstrating the effect of n-3 PUFAs on the long-term cardiovascular prognosis of these patients.

Neuroprotective action of n-3 polyunsaturated fatty acids

n-3 PUFA intake is associated with reduced risk of age-related cognitive decline [44]. n-3 PUFAs are highly concentrated in the mammalian central nervous system and enhance synaptic activities in neuronal cells. They attenuate brain necrosis after hypoxic ischemic injury, principally by modulating membrane biophysical properties and maintaining integrity in functions between presynaptic and postsynaptic areas, resulting in better stabilization of intracellular ion balance in hypoxic-ischemic insult. Additionally, they alleviate brain apoptosis, by inducing antiapoptotic activities such as decreasing responses to reactive oxygen species, upregulating antiapoptotic protein expression, downregulating apoptotic protein expression, and maintaining mitochondrial integrity and function [45]. Clinical evidence shows that n-3 PUFAs could prevent stroke recidivisms [46], and inhibit symptomatic cerebral vasospasm and cerebral infarction after subarachnoid hemorrhage [47].

Beyond some preliminary evidence of efficacy [48], more recent trials carried out with DHA alone in Alzheimer disease patients did not show any delaying action of n-3 PUFAs against cognitive decline [49]. This observation could be influenced by the patient selection, the use of DHA alone, the timing of intervention and/or by the relatively short observation period. However, a lack of effect of n-3 PUFAs on cognitive decline has also been observed in the Alpha Omega Trial [50], where underdosed EPA and DHA were used, as well. Even if n-3 PUFA supplementation is associated with a significant reduction in brain atrophy in Huntington disease patients, particularly in the caudate and thalamus [51], they seem not to be effective in improving their cognitive function [52]. So, current available clinical evidence does not support the use of n-3 PUFA to slow cognitive decline in patients with neurodegenerative disorders, despite some positive data in subjects with mild cognitive disorders due to different causes [53].

Antithrombotic effects

Aspirin resistance is associated with unfavorable prognosis, including a higher incidence of myocardial infarction, stroke, and cardiovascular death among stable cardiovascular patients, a higher incidence of re-occlusion after peripheral angioplasty, and myonecrosis following elective percutaneous coronary interventions (PCI) [54]. The antithrombotic effect of n-3 PUFAs is still under evaluation, but it also seems to be dose-related [55]. In particular, n-3 PUFAs decrease thrombin formation and oxidative stress and favorably alter fibrin clot properties, at least in stable coronary artery disease patients undergoing percutaneous coronary intervention [56]. Always in percutaneous coronary revascularization patients, n-3 PUFAs added to the combination of aspirin and clopidogrel significantly potentiates the platelet response to clopidogrel [57]. Moreover, adding n-3 PUFAs to low-dose aspirin reduces aspirin resistance similarly to increase of aspirin dose [58]; this could have some positive effects in terms of gastrointestinal tolerability of aspirin, beyond all the other known n-3 PUFA actions. n-3 PUFAs could also exert some favorable effect in patients affected by prothrombotic conditions such as sickle cell disease [59].

n-3 Polyunsaturated fatty acids in rheumatological diseases and osteoporosis

Rheumatological and, more generally, inflammatory conditions are associated with an increased risk of cardiovascular disease, related to arrhythmias [60], metabolic factors [61], or systemic inflam-

mation [62]. n-3 PUFAs decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species and the expression of adhesion molecules; they act both directly (e.g., by replacing arachidonic acid as an eicosanoid substrate and inhibiting arachidonic acid metabolism) and indirectly (e.g., by altering the expression of inflammatory genes through effects on transcription factor activation), also giving rise to a family of anti-inflammatory mediators, the resolvins [63]. Thus, n-3 PUFAs are potentially potent anti-inflammatory agents. Clinically their use is associated with a reduction in the need of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with rheumatoid arthritis [64], with obvious consequences in terms of gastrointestinal safety. Meta-analytic data show that supplementation with n-3 PUFAs for 3-4 months reduces patient reported joint pain intensity (standardized mean difference [SMD]: –0.26; 95% CI: –0.49 to –0.03, p = 0.03), minutes of morning stiffness (SMD: –0.43; 95% CI: –0.72 to –0.15, $p = 0.003$), number of painful and/or tender joints (SMD: –0.29; 95% CI: –0.48 to –0.10, $p = 0.003$), and NSAID consumption (SMD: –0.40; 95% CI: –0.72 to –0.08, $p = 0.01$) [65]. n-3 PUFAs also have a positive impact on the metabolic pattern, the endothelial function and the disease activity in systemic lupus erythematosus patients [66]. Thus, n-3 PUFAs improve metabolic pattern and reduce systemic inflammation in rheumatological disorders. The anti-inflammatory effects are also evident in other inflammatory conditions such as chronic bowel diseases [67] and asthma [68].

Osteoporosis and cardiovascular diseases have emerging epidemiological and physiopathological links [69]. There are different mechanisms by which dietary fatty acids affect bone: effects on calcium balance, effects on osteoblastogenesis and osteoblast activity, change of membrane function, decrease in inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α), and modulation of peroxisome proliferator-activated receptor gamma (PPAR-γ) [70]. Emerging epidemiological evidence also supports an anti-osteoporotic effect of n-3 PUFAs [71], and preliminary data derived from small clinical trials suggest that n-3 PUFAs decrease bone reabsorption but do not increase new bone formation [72]. A recent randomized clinical trial showed that n-3 PUFA supplementation is synergistic with long-term aerobic exercise training in attenuating inflammation and augmenting bone mass density in postmenopausal osteoporosis [73].

Depression

Depression is also a widely prevalent (and often undetected) condition in internal medicine patients [74]. Depression is an independent risk factor for coronary heart disease and for its recidivism, so that recently the American Heart Association has recommended a 2-step screening method, consisting of the 2-item Patient Health Questionnaire (PHQ-2) followed by the 9-item Patient Health Questionnaire (PHQ-9), for identifying depression in cardiovascular patients [75]. A recent meta-analysis of 29 randomized clinical trials showed that the pooled standardized difference in mean outcome was 0.10 SD (95% CI: 0.02, 0.17) in those who received n-3 PUFAs compared with placebo. Greater effects of n-3 PUFAs were found in individuals with more severe depressive symptoms. In trials that enrolled individuals with a diagnosed depressive disorder, the combined mean difference was 0.41 (95% CI: 0.26, 0.55), while in trials that enrolled individuals without a depressive diagnosis, no beneficial effects of n-3 PUFAs were found. The large heterogeneity among trials could be related to variation in patients' characteristics [76]. For instance, n-3 PUFAs exert a specific antidepressant activity in perimenopausal women, in whom they also reduce the incidence of hot flushes and reduce the triglyceride levels, which usually increase after menopause [77]. Moreover, the n-3 PUFA antidepressant effect seems also to be particularly evident in the elderly, where 2-month treatment with 2.5 g/day has been associated with improvement of the Geriatric Depression Scale (GDS) and of the physical and mental components of the Short-Form 36-Item Health Survey (SF-36) [78]. Similar results have been observed in Parkinson's disease, as well [79]. But the tested product could also strongly influence the observed effect: a further recent meta-analysis in fact suggests that EPA has greater n-3 PUFA antidepressant action than DHA [80].

Tolerability and safety data

Side effects such as fishy aftertaste are uncommon, and gastrointestinal complaints are infrequent at moderate intakes, and reduced when esterified n-3 PUFAs are used [81]. Some reports show that fish oil may worsen glycemic control in diabetes, but recent data indicate that this adverse effect is not common when diabetics are adequately treated [82]. However, data from the Women's Health Initiative show that PUFA intake higher than 2 g/day is associated with a significant increase in type 2 diabetes incidence [83]. Concerns have also been raised regarding adverse effects on LDL cholesterol plasma level and oxidative stress, but increases in LDL cholesterol are modest and studies into oxidative stress have been contradictory. Overall these effects are unlikely to be dominant given the apparent cardiac benefits of n-3 PUFAs [84]. Therefore, n-3 PUFAs may exert a dose-related effect on bleeding time, but an objective assess-

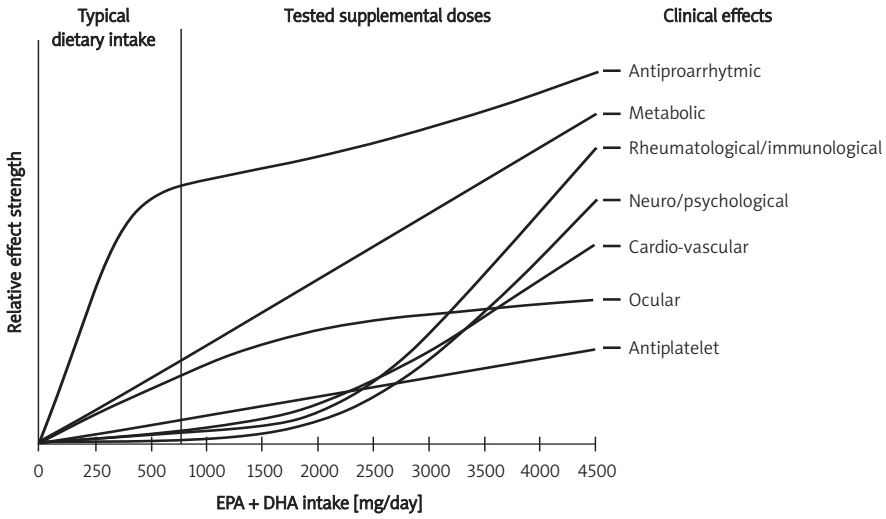

Figure 1. Dose-dependent clinical effects of polyunsaturated omega 3 fatty acids

ment of the evidence for clinically significant bleeding reveals that such concerns are unfounded [85].

More specific concerns regarding dietary fish relate to environmental contaminants, and mercury in fish may attenuate their cardioprotective effects [86]. However, a risk-benefit analysis of changes in population fish consumption concluded that reduced fish intake because of poisoning fear has a negative net public health impact [87]. Moreover, contaminants accumulate in larger, predatory fish, and consumption of a variety of fish (or of fish oil supplements) should minimize any possible adverse effects. On the other hand, consumption of equal amounts of EPA and DHA from oily fish weekly or in the form of capsules daily are nearly equally effective [88], whereas capsules are usually safer as regards possible contaminant contents, and they are not a source of other fatty acids or energy. Finally, no significant negative interaction has been observed as yet between most drugs and PUFAs [89], the only exception being a small increasing effect of anticoagulant drugs with the use of large doses [90].

Discussion

A large number of preclinical studies and some preliminary evidence suggest a therapeutic potential of n-3 PUFAs in a wide number of diseases. In some cases, the evidence quality is low and limited to single underpowered trials [91]. However, for some specific diseases, widely prevalent in internal medicine practice, and directly or indirectly related to cardiovascular disease risk, some strong evidence supports the usefulness of adequately dosed n-3 PUFAs. Beyond their known direct cardiometabolic effects, they appear to be safe and useful therapeutic tools for patients with conditions that per se could increase the cardiovascular disease risk of patients (such as CKD, NASH, depression, treatment with HAART and others) or to improve specific aspects of the conditions themselves (such as depressive traits, CKD progression, or liver fibrosis). What has to be underlined is that the greater part of the observed effect is dose-related and the PUFA amount in a standard diet or the single gram of PUFAs prescribed to post-infarction patients in order to reduce their arrhythmia risk is probably not sufficient to achieve all the PUFA relevant effects (Figure 1). Moreover, the quality of the tested products and the adequate balance between EPA and DHA is another factor strongly affecting the efficacy of this approach. However, in the cost-benefit ratio, we also have to consider that n-3 PUFAs could have positive effects not directly related to cardiovascular disease risk, but on very frequent conditions that can be routinely observed in internal medicine patients, such as sarcopenia [92], macular degeneration and other eye disturbances [93], psychotic disorders [94], chronic respiratory diseases [95, 96], relapsing-remitting multiple sclerosis [97], cutaneous wounds [98], and atopic eczema [99].

On the other hand, other studies do not support some indications for n-3 PUFA supplementation in specific conditions, for instance La Peyronie's disease [100], Crohn's disease [101], autosomal dominant polycystic kidney disease [102], pediatric asthma [103], and refractory epilepsy [104].

When treating patients with increased cardiovascular risk with n-3 PUFAs, in order to obtain the best cost-benefit ratio taking into account any comorbidities, one has to consider the adequacy of the prescribed formulation and the correct dosage employed. However, larger studies need to be carried out to determine whether n-3 PUFA sup-

plementation could decrease the cardiovascular risk associated with all the potential clinical indications.

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