Lipids and physical function in older adults

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Purpose of review

Healthy aging is a public health priority. The maintenance of adequate physical function is recognized as a key element of healthy aging. In recent years, scientific evidence has increased concerning the ability of lipids, in particular omega 3 polyunsaturated fatty acids (n-3 PUFAs), to positively influence muscle and overall physical function in older patients. The article will critically review observational as well as intervention studies on this topic, and it will elucidate the potential biological mechanisms underlying the beneficial effects of n-3 PUFA on physical function.

Recent findings

Observational studies and clinical trials performed in healthy older patients and in older patients with chronic diseases mostly found positive effects of n-3 PUFA on muscle metabolism, muscle strength and in general physical function.

Summary

Although the use of n-3 PUFA might represent an important intervention to preserve physical function in older adults, several key questions still need to be answered. Above all, large randomized controlled trials should be performed to confirm the utility of n-3 PUFA as therapeutic agents to prevent and treat physical function decline in old age.

Keywords

aging, lipid, n-3 polyunsaturated fatty acid, physical function, sarcopenia

KEY POINTS

- Physical function is a key component of healthy aging.

- n-3 PUFA supplementation has been shown in observational and intervention studies to improve muscle performance and physical function, mainly in healthy older people.

- Large-scale clinical trials are necessary to confirm that these beneficial effects can be obtained in the general older population, including patients with multimorbidity and frailty.

INTRODUCTION

Healthy aging is public health priority in our society [1]. The WHO report on aging and health defines healthy aging as 'the process of developing and maintaining the functional ability that enables well-being in older age', acknowledging that the ability to function is the most important aspect of health in the older population. Function can be viewed as a summary measure of the overall effect of aging-related changes, lifestyle and diseases, in the context of the environment and social support. A great deal of attention is currently devoted to identify the determinants of healthy aging. Nutrition is considered one of the principal factors influencing aging-related and age-related diseases. Among nutrients, the role of proteins has been extensively investigated [2], whereas other substances, for example lipids, have received less consideration. Lipids are molecules whose biological functions include energy storage, signaling and acting as structural components of cell membranes. Recently, a number of studies investigated the potential role of lipids, in particular polyunsaturated fatty acids (PUFAs), in counteracting physical function impairment, which is often related to the loss of muscle mass and function with aging, that is sarcopenia, in older patients. In this review, we will critically examine the scientific literature on this topic and highlight areas that deserve further investigation.

POLYUNSATURATED FATTY ACID AND PHYSICAL FUNCTION: OBSERVATIONAL STUDIES

PUFA contain more than one double bond. The most important PUFA are omega-3 (n-3) and omega-6 (n-6) PUFA. The former include alpha linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), whereas the latter include linoleic acid and arachidonic acid. ALA and linoleic acid cannot be synthetized by the human body and therefore are essential nutrients. Observational studies performed during the last decade suggest a potential role of n-3 PUFAs in the preservation of muscular and physical function in older adults [3–8,9&–11&]. Dietary intake of PUFAs in relationship to muscle and physical performance has been investigated in different populations. In the Hertfordshire study, Robinson et al. [3] estimated the average consumption of foods and assessed muscle function. In both sexes, the most important food positively associated with grip strength was fatty fish. In Japanese communitydwelling patients of 85 years of age a lower

habitual intake of EPA and DHA was associated with poor functional mobility in men but not in women [7]. The higher proportion and severity of patients with cognitive impairment among women could explain this sex difference [7]. At variance, Rousseau et al. [5] found an association between self-reported dietary intake of n-3 PUFA and physical performance, which was not confirmed in the multivariable analysis. Another approach to examine the role of PUFA is to measure their levels in plasma [4,6,8,9&– 11&]. Plasma FAs are good markers of dietary intake. These studies found a positive correlation between circulatory levels of n-3 PUFA and physical capacity measured as walking speed [4] and muscle strength [4,10&] in older adults. In the InCHIANTI study, older patients with impaired lower extremity performance, defined as a short physical performance battery score less than 9, had lower plasma levels of total PUFA, n-3 and n-6 FAs. Moreover, participants who experienced a decline in physical performance during the follow-up had lower baseline levels of n-3 PUFA and higher n-6/n-3 ratio [4]. Similarly, in a population-based sample of French older adults, a higher percentage of long chain n-3 levels was associated with a lower probability to have reduced gait speed, whereas a higher ratio between arachidonic acid and n-3 PUFA in plasma was positively related to lower walking speed [9&]. Finally, n-3 PUFAs were associated with larger muscle size and greater knee extensor strength [11&] and prospectively with lower risk of mobility disability in women but not in men in a cohort study in Iceland [10&]. No association was observed between plasma n-3 PUFAs or n-6 PUFAs and decline in gait speed [10&]. The levels of long chain n-3 PUFA were significantly lower in cancer patients with sarcopenia [6]. The majority of observational studies found a relationship between long chain n-3 FAs and physical function, although some negative results have been reported and the association was not consistently found in both sexes. The relationship has been confirmed by direct measurement of levels of FAs, in longitudinal analysis with a long followup, and in different populations. Nevertheless, no study measured FAsmore than once, and therefore it is not possible to examine the relationship between changes in levels of FAs and modifications of physical function. The main characteristics of observational studies are described in Table 1.

POLYUNSATURATED FATTY ACID AND PHYSICAL FUNCTION: CLINICAL TRIALS

Clinical trials in healthy older patients [12– 15,16&&,17&&,18&] and in older patients suffering from a chronic disease [19,20] have mostly demonstrated that n-3 PUFA improve muscle performance and physical function. Supplementation with 1.2 g/day of fish oil during 6-months in prefrail older women improved walking speed, but not hand grip or lower limb strength [14]. A recent study evaluated the effects of the supplementation of high doses n-3 PUFA (4 g/day) for 6 months, showing an improvement in muscle mass and performance in older adults [17&&]. In older women, fish oil supplementation increased resting metabolic rate, exercise-related energy expenditure, lean body mass and improved functional capacity [16&&]. On the contrary, some authors did not find any beneficial effects of n-3 PUFA on muscle mass, muscle strength and physical performance [15]. Positive results were also obtained in small clinical studies performed in older patients with different diseases. In patients suffering from chronic obstructive pulmonary disease, PUFA supplementation increased the effects of exercise training, in terms of peak exercise capacity and submaximal endurance time [19]. Few studies assessed the combined effect of exercise and n-3 PUFA. Overall, the effect of exercise training seems stronger than that of PUFA in increasing lean mass, muscle performance and physical capacity. Rodacki et al. [13] found that n-3 PUFA supplementation in combination with strength training significantly increased muscle strength and functional capacity gains compared with strength training alone in older women. However, n-3 supplementation alone before strength training did not have any effect [13]. At variance, resistance training increased muscle strength independent from the intake of PUFA, although an improvement in the skeletal muscle mass occurred only when it was combined with a healthy diet (with a n-6/n-3 ratio <2) [18&].As n-3 PUFAs improvemuscle strength, it could be assumed that they also increase muscle mass. However, intervention studies provided conflicting results on this aspect [21&&]. A likely explanation of this inconsistency might be the short duration of many trials and, in some of them, the insufficient amount of n-3 PUFA used, as it appears that a minimum dose of 2 g/day is needed to stimulate muscle anabolism. Furthermore, the method used to measure muscle mass is relevant: dual radiograph absorptiometry and bioelectrical impedance analysis assess whole lean body mass, only half of which is represented by muscle and might therefore be unable to detect small changes in muscular mass. The main characteristics of intervention studies are described in Table 2.

POLYUNSATURATED FATTY ACID AND PHYSICAL FUNCTION: BIOLOGICAL MECHANISMS

The biological mechanisms by which PUFA improve muscular and physical function have been investigated but are not entirely clear yet. FAs have multiple functions at cellular level, being major components of membranes and being involved in several metabolic processes, by regulating the activity of enzymes and acting as signaling molecules. The available evidence suggests that n-3 PUFAs are active at muscular level, in which they could increase the synthesis and decrease the breakdown of proteins [22]. PUFAs seem to counteract the blunted anabolic response to stimuli, for example protein intake and exercise, the so-called anabolic resistance, which contributes to the occurrence of sarcopenia in older patients. In a seminal article, Smith et al. demonstrated that PUFAs stimulate protein synthesis not in the basal state but during hyperaminoacidemia and hyperinsulinemia condition. This activity was associated with an increased activation of the mechanistic target of rapamycin (mTOR) pathway [23]. The same authors investigated whether n-3 PUFA supplementation is able to increase the expression of genes involved in the regulation of mitochondrial function and anabolic pathways as well as decrease the expression of genes related to autophagy and atrophy of muscles [24&&]. They found that several genes involved in respiratory electron transport and oxidative phosphorylation, that is mitochondrial function, were increased. At the same time, pathways involved in calpain-mediated and ubiquitin-mediated proteolysis, mRNA translation and inhibition of mTOR signaling were significantly decreased by n-3 PUFA. Overall, the changes observed were modest, suggesting that n-3 PUFA may induce small changes in the muscle [24&&]. Interestingly, in animal models, n-3 PUFA have shown to reduce the rate of protein degradation, likely by means of the inhibition of the nuclear factor kappa B (NF-kB) pathway [22]. Other mechanisms have been proposed. When n-3 PUFAs are introduced, cell membranes of different tissues including the skeletal muscle incorporate them. This fact has been shown in human studies [25,26]. In addition, higher amounts of Ca2þ-ATPase and Naþ/Kþ-ATPase proteins might explain the increase in metabolic rate following n-3 PUFA ingestion [27]. n-3 PUFA may improve mitochondrial functions by modulating nuclear gene expression and the mitochondrial membrane. In the nucleus, n-3 PUFA might affect the expression of genes regulating the energy metabolism and

mitochondrial function such as the peroxisome proliferator–activated receptor gamma coactivator 1-alpha [28&]. In parallel, the activation of peroxisome proliferator–activated receptors (PPARs) may result in changes in energy metabolism by influencing mRNA, protein expression and the activity of various proteins. Furthermore, n-3 PUFA have been shown to increase the expression of genes involved in extracellular matrix organization, which are involved in the development and maintenance of the muscle [24&&]. The beneficial effect of PUFAs on the muscle and physical function could be explained in part by their anti-inflammatory properties [29]. First of all, they compete with n-6 PUFA, in particular arachidonic acid, as substrate for enzymes, such as cyclooxygenase and lipoxygenase that produce eicosanoids. Of note, the eicosanoids produced from n-3 PUFA are less powerful proinflammatory agents than those derived from arachidonic acid, and n-3 PUFAs are precursors of inflammation resolving molecules [29]. In this respect, it seems that the ratio of n-6 to n-3 PUFA in the diet might be important to reduce inflammation. Moreover, n-3 PUFA can decrease the synthesis of proinflammatory cytokines by binding to nuclear receptors. They prevent the degradation and subsequent translocation of the NF-kB complex to the nucleus in which it induces transcription of inflammatory cytokines. The reduction in NF-kB pathway activation is thought to be caused by an up-regulation in PPARg activity. In addition to direct action at the muscular tissue, n-3 PUFA could improve peripheral neuromuscular function, increasing muscle activation [30], nerve conduction velocity and the sensitivity to acetylcholine, which stimulates the contraction of the muscle [22].

DISCUSSION

The majority of studies found beneficial effects of n-3 PUFA intake and supplementation on muscle mass, muscle strength and physical function in older patients. Several mechanisms are likely to explain the ability of n-3 PUFA to improve physical function. The most consistent effects of n-3 PUFA supplementation is at the muscular level. First of all, they have a direct anabolic effect on the muscle that has been demonstrated also in older adults. n-3 PUFA might also reduce protein catabolism, although evidence in humans is limited. Mitochondrial function is enhanced by n-3 PUFA, through different actions. A large body of research supports an important anti-inflammatory

activity of n-3 PUFA, but its contribution to the positive effects on the muscle has still to be confirmed in humans. Up to now, the majority of clinical trials did not find changes in inflammatory markers, possibly because they included relatively healthy older patients, whose level of systemic inflammation was normal. Nevertheless, also in prefrail older women n-3 PUFA did not modify the levels of inflammatory markers [14]. Finally, an improvement of neuromuscular function might occur during supplementation. Although the positive effects of n-3 PUFA have been confirmed in different trials, there are several limitations in the available scientific evidence. First of all, the majority of trials included relatively healthy older patients or patients with a specific chronic disease. It would be extremely relevant to confirm the possibility to improve muscle function and physical performance also in older adults who are suffering from multimorbidity, frailty and sarcopenia as the current therapeutic strategies for this group are limited, that is exercise and nutritional interventions, which consist of protein and vitamin D supplementation [31,32&&]. Moreover, it would be important to explore the potential benefits of n-3 PUFA in older patients who experience an accelerated muscle and functional loss, for example due to periods of forced immobilization. Although the optimal dose of n-3 PUFA is not known, the majority of clinical trials investigated the effect of moderate or high dose supplements of long chain n-3 FAs, that is doses equal or above 1 g/day of EPA and DHA. These doses are higher than those currently recommended for healthy patients. As the intake of n-3 PUFA is currently low in the majority of the population, the possibility to considerably increase the consumption of foods rich in long chain n-3 PUFA, that is fish, in particular fatty fish such as salmon, herring, halibut and mackerel, could be challenging. In this respect, supplementation might be the only effective strategy to achieve the desired intake. Another related but distinct issue is whether ALA, the precursor of long chain n-3 PUFA, might have similar effects on the muscle and on physical function. ALA, which is the most abundant n-3 FA in the Western diet, is present in vegetable oils and nuts, flax seeds and flaxseed oil, leafy vegetables and some animal fat. However, this question cannot be answered yet, as in the only study that evaluated a high dose of ALA supplement, the participants were also participating in a strength training program [18&]. Although available data suggest that the effect of exercise on the muscle and on physical function is greater than that of n-3 PUFA, the combination of these two interventions has been tested in very few studies. All these

points represent relevant topics that deserve further investigation. Finally, large-scale randomized controlled trials need to be performed to evaluate whether n-3 PUFA treatment can postpone the onset or slow the progression of physical function decline in older adults, using clinically relevant outcomes in this population, such as the prevention or recovery of mobility disability [33&].

CONCLUSION

The available evidence suggests that n-3 PUFA might be a promising treatment to prevent and treat physical function impairment in older patients. However, large-scale clinical trials are needed to confirm this hypothesis.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:
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Table 1. Observational studies that investigated the relationship between n-3 polyunsaturated fatty acid intake or plasma levels and measures of muscle mass, muscle strength and physical function

Reference	Study design	Population	Age (years)	Sex distribution % female	Sample size	Main results
Robinson *et al.* [3]	Cross-sectional and retrospective cohort study	A large cohort of community-dwelling elderly individuals from the Hertfordshire Cohort Study	59–73	47.4	2983	Higher fatty fish consumption was associated with higher grip strength
Abbatecola *et al.* [4]	Cross-sectional and prospective	A population-based study of older Italians from the InCHIANTI study	68.8 ± 15.7	55.7	1273 (baseline) 884 (at follow-up)	At baseline higher plasma n-3 PUFA concentrations were associated with higher walking speed After a 3-years period: higher baseline plasma n-3 PUFA levels were associated with lower risk of declining physical performance, whereas n-6/n-3 ratio was associated with higher risk A higher n-6/n-3 ratio was associated with a longer time to walk 7 m, whereas total PUFA and n-3 PUFA were associated with faster walking speed
Rousseau *et al.* [5]	Cross-sectional	Older adults residing in the community or an assisted living facility	78.9 ± 6.8	52.2	247	Self reported n-3 FA intake was associated with physical performance in the univariate analysis but the association was not confirmed in the multivariate analysis
Murphy *et al.* [6]	Cross-sectional	Patients with cancer from the nonsmall cell lung cancer cohort	62 ± 1.4	53.6	41	Individuals with low plasma n-3 PUFAs had lower muscle mass and greater muscle mass loss than individuals with higher n-3 PUFAs
Takayama *et al.* [7]	Cross-sectional	Japanese community-dwelling oldest old	86-89	56.2	495	A lower habitual intake of EPA + DHA was significantly associated with poor functional mobility in men but not in women Men showed a significant inverse correlation between inflammatory biomarkers and TUG performance, and likewise, an inverse correlation between inflammatory biomarkers and marine-origin n-3 PUFA intakes
Welch *et al.* [8]	Cross-sectional	Healthy free-living women from the TwinsUK Study	18–79	100	2689	A higher PUFA to SFA ratio was associated with greater FFM and FFMI

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Table 1 (*Continued*)

Reference	Study design	Population	Age (years)	Sex distribution % female	Sample size	Main results
Frison *et al.* [9•]	Crosssectional	A French community-dwelling older adults of the Three-City-Bordeaux study	65	59.1	982	High plasma concentrations of LC n-3 PUFAs was associated with higher gait speed in community-dwelling older adults, whereas a higher AA/(EPA + DHA) ratio was associated with lower gait speed
Reinders *et al.* [10•]	Crosssectional and prospective	Older adults from the Age, Gene/Environment Susceptibility–Reykjavik Study	76.7 ± 5.6	53.6	836 (cross-sectional analysis)	Higher plasma concentrations of PUFAs, especially EPA and DHA, were associated with larger muscle size and greater knee extension strength
			74.9 ± 4.9	54.3	459 (prospective analysis)	After a 5.2-years period, α-linolenic acid was positively associated with increased knee extension strength
Reinders *et al.* [11•]	Prospective	Older adults from the Age, Gene/Environment Susceptibility–Reykjavik Study	75.1 ± 5.0	52.5	556	Higher plasma phospholipid long-chain n-3 PUFAs, and in particular DHA, were associated with lower risk of mobility disability in women but not in men after 5-year of follow-up
						No associations were observed for plasma phospholipid long-chain n-3 PUFAs with decline in gait speed
						Plasma phospholipid long chain n-6 PUFAs were not associated with mobility disability or decline in gait speed

AA, arachidonic acid; DHA, docosahexanoic acid; EPA, eicosapentanoic acid; FA, fatty acid; FFM, fat-free mass; FFMI, fat-free mass index; LC, long-chain; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; TUG, Timed Up and Go test.

TABLES

Table 2. Interventional studies that investigated the effects of n-3 polyunsaturated fatty acid on muscle mass and strength and physical function

Reference	Type of study	Population	Age (years)	Sex distribution % female	Sample size	Study duration	Intervention	Main results
Broekhuizen *et al.* [19]	Double blind randomized trial	Patients with COPD	63 ± 9	43.7	102	8-weeks	Patients received 9 capsules (9 kcal/capsule) daily of: PUFA capsules: the daily dosage of PUFA consisted of 3.4 g active FAs, a blend of 400 mg STA, 760 mg GLA, 1200 mg ALA, 700 mg EPA and 340 mg DHA Placebo capsules: 80% palm oil and 20% sunflower oil	n-3 PUFA therapy increased endurance and peak workload during cycling exercise compared with placebo group
Cornish and Chilibeck [12]	Randomized controlled trial	Healthy older adults	65.4 ± 0.8	45.1	51	12-weeks	ALA supplement of 30 ml of flaxseed oil (~14 g/day of ALA) + resistance training 3 day/week Placebo supplement (corn oil) + resistance training 3 day/week	ALA supplementation with resistance training exposure resulted in only minimal improvement of lean tissue mass and muscle strength in comparison with resistance training alone
Sinn *et al.* [20]	Double-blind randomized controlled trial	Elderly people with MCI	>65	32.0	50	6-month	EPA-rich FO: 1.67 g EPA + 0.16 g DHA/day DHA-rich FO: 1.55 g DHA + 0.40 g EPA/day Sunflower oil: 2.2 g LA (n-6 PUFA)/day (control)	Increased DHA was significantly associated with improved self-reported physical health but not functioning on the healthy survey SF-36
Rodacki *et al.* [13]	Randomized controlled trial	Elderly women	64 ± 1	100	45	90–150 days	Strength training only for 90 days Strength training + supplementation with FO (2 g/day with 1.2 g EPA and 0.9 g of DHA) for 90 days FO supplementation (2 g/day with 1.2 g EPA and 0.9 g of DHA) 60 days before commencing the strength training for 90 days	n-3 PUFA supplementation in combination with strength training significantly improved muscle strength (knee flexor and extensor, plantar and dorsi-flexor) and functional capacity (chair-rising performance) of older women. However, n-3 supplementation alone for an additional period pretraining did not cause any effect

Table 2 (*Continued*)

Reference	Type of study	Population	Age (years)	Sex distribution % female	Sample size	Study duration	Intervention	Main results
Hutchins-Wiese *et al.* [14]	Double-blind, randomized controlled trial	Postmenopausal women	75 ± 7	100	126	6-month	Supplementation with FO (1.2 g/day with 0.72 g EPA and 0.48 g DHA) capsules per day Placebo supplementation with olive oil (1.8 g oleic acid/day)	Supplementation with FO improved walking speed compared with placebo, but was ineffective in terms of muscle strength
Smith *et al.* [17**]	Double-blind, randomized controlled trial	Healthy older people	60–85	ND	60	6-month	n-3 PUFA therapy that provided a total of 1.86 g EPA and 1.50 g DHA Placebo control with corn oil	n-3 PUFA therapy increased thigh muscle volume, the handgrip strength, and 1-repetition maximum strength and tended to increase average isokinetic power compared with the control group
Logan and Spriet [16**]	Randomized controlled trial	Healthy community dwelling older women	66 ± 1	100	24	12 weeks	FO supplementation: 5 g/day of FO (2 g/day EPA and 1 g/day DHA) Placebo supplement: 3 g/day of olive oil	FO supplementation compared with placebo group: Increased RMR by 14%, EE during exercise by 10%, and the rate of fat oxidation during rest by 19% and during exercise by 27% Decreased triglyceride levels by 29% and increased lean mass by 4% and functional capacity by 7%
Krzyminska-Siemaszko *et al.* [15]	Randomized controlled trial	Elderly people with DMM	74.6 ± 8.0	67.9	53	12 weeks	PUFA-treated groups received 1.3 g of n-3 PUFA. [2 capsules daily containing 660 mg EPA, 440 mg DHA + 200 mg other n-3 FAs + 10 mg of vitamin E) Control groups received 1 drop of vitamin E solution (11 mg) daily	n-3 PUFA supplementation did not significantly affect body composition, muscle strength or physical performance

Table 2 (*Continued*)

Reference	Type of study	Population	Age (years)	Sex distribution % female	Sample size	Study duration	Intervention	Main results
Strandberg *et al.* [18•]	Three armed randomized controlled trial	Healthy and physically active older women	65–70	100	63	24-weeks	Control group A resistance training group A resistance training and healthy diet group with an n-6/n-3 ratio <2	Resistance training improved muscle strength Resistance training combined with a healthy diet (with a n-6/n-3 ratio <2) improved the skeletal muscle mass

ALA, alpha-linolenic acid; COPD, chronic obstructive pulmonary disease; DHA, docosahexanoic acid; DMM, decreased muscle mass; EE, energy expenditure; EPA, eicosapentanoic acid; FA, fatty acid; FO, fish oil; GLA, gamma-linolenic acid; LA, linoleic acid; MCI, mild cognitive impairment; ND, no described; PUFA, polyunsaturated fatty acid; RMR, resting metabolic rate; STA, stearidonic acid.