Clinical Nutrition 39 (2020) 23–32

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Review

Is there sufficient evidence to supplement omega-3 fatty acids to increase muscle mass and strength in young and older adults?

Luana T. Rossato [a], Brad J. Schoenfeld [b], Erick P. de Oliveira [a, *]

[a] School of Medicine, Federal University of Uberlandia (UFU), Uberlandia, Minas Gerais, Brazil
[b] CUNY Lehman College, Department of Health Sciences, Bronx, USA

ARTICLE INFO

Article history:
Received 12 November 2018
Accepted 2 January 2019

Keywords:
Omega-3
Muscle protein synthesis
Muscle mass
Lean mass
Physical function

SUMMARY

Omega-3 (ω-3) is a polyunsaturated fatty acid with anti-inflammatory properties that presents three main forms: alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid. Recently, studies performed in both young and older adults suggest that ω-3 may improve gains in muscle mass and/or enhance physical function. Thus, the aim of this narrative review was to evaluate the current evidence of ω-3 intake/supplementation on muscle/lean mass (LM) and physical function in young and older adults, and draw research-based conclusions as to the practical implications of findings. We first assessed whether ω-3 intake is associated with muscle mass and strength (observational studies), and then sought to determine whether evidence shows that supplementation of ω-3 increases muscle protein synthesis, LM and strength in adults and older adults (interventional studies). The search was carried out in PubMed and Scopus databases for the periods between 1997 and November 2018. The following keywords were used alone and in combination: ω-3, fish oil, muscle protein synthesis, muscle mass, lean mass, body composition, and physical function. In general, the evidence is mixed as to the effects of ω−3 supplementation on muscle mass in sedentary young and older adults; the hypertrophic effects of supplementation when combined with resistance training remain equivocal. Moreover, there is conflicting evidence as to whether supplementation confers a beneficial effect on muscle function in older adults. Importantly, this conclusion is based on limited data and more studies are needed before ω-3 supplementation can be recommended as a viable strategy for such purposes in clinical practice.

1. Introduction

Omega-3 fatty acids (ω-3) are polyunsaturated fatty acids (PUFA), which are a family of essential fatty acids that mediate numerous biological processes. There are three major dietary forms of ω-3: alpha-linolenic acid (ALA; 18:3n-3), eicosapentaenoic acid (EPA; 20:5n-3), and docosahexaenoic acid (DHA; 22:6n-3). ALA is considered an essential dietary fatty acid, meaning it cannot be synthesized in humans [1]. It is found in a relatively limited set of foods including nuts, seeds, and their oils (mainly in flaxseed and chia) [2]. Although there are some biochemical pathways to convert ALA into EPA and DHA, a limitation for this endogenous conversion is observed in humans (DHA conversion is even lower than EPA conversion) [3,4]. Thus, circulating and tissue levels of EPA and DHA are mainly determined by dietary consumption [1,5], with fish oil (FO) being the major dietary source of EPA and DHA [2]. Supplements containing FO are mainly composed of triglycerides, ethyl esters, and phospholipids, as well as frequently containing additional essential micronutrients such as vitamins D and E [6]. Various global recommendations indicate that ω-3 intake should be ~1 g per day [7–9]. Many expert committees in the primary prevention of coronary heart disease recommend approximately 2 servings of fatty fish per week, which represents a combined ~500 mg of EPA and DHA per meal [10,11]. It is important to draw attention to the fact that the modern Western diet had several potentially detrimental effects on health as a result of high consumption of saturated fats and ω-6, with a corresponding low intake of ω-3 [12]. When the adequate consumption of a certain nutrient is not possible or does not occur through food consumption, supplementation is required for diet adequacy [13].

* Corresponding author. Av. Pará, no1720 Bloco 2U Campus, Uberlândia, Umuarama, 38400-902 MG, Brazil.
E-mail address: erick_po@yahoo.com.br (E.P. de Oliveira).

https://doi.org/10.1016/j.clnu.2019.01.001
0261-5614/

Table 1
Studies assessing the effects of ω-3 on muscle protein synthesis (MPS), lean/fat-free mass and muscle function in young individuals.

Author	Year	Study design	n (m/w)	Intervention	Control	Diet	Exercise	Time	Mainly results
Smith et al.	2011	RCT	9 (5/4)	1.86 g EPA + 1.5 g DHA	NC	NC	NC	8wk	ω-3 increased MPS, and also doubled the anabolic response to amino acid and insulin infusion.
McGlory et al.	2016	RCT, double-blind, controlled	19 (19/0)	3.5 g EPA + 900 mg DHA + 100 mg DPA + 0.1 mg vitamin E	5 g coconut oil	3-d food diary	1 acute session	8wk	MPS increased similarly between conditions post-exercise; however, the activity of p70S6K1 was elevated 3h after the resistance exercise following protein ingestion only in the coconut oil group
Couet et al.	1997	Clinical trial	6 (5/1)	6 g fish oil	6 g other fats	7-d food diary	NC	3wk (each intervention)	No change in FFM was found for either condition.
Sneddon et al.	2008	Crossover, double-blind, placebo-controlled	59 (59/0)	2.28 g CLA + 900 mg EPA + 630 mg DHA	4.8 g palm oil + 1.2 g soya bean oil	NC	NC	12wk	CLA + ω-3 treatment increased FFM (1.3%) in young obese men, but not in lean young adults.
Noreen et al.	2010	RCT, double-blind, controlled	44 (14/30)	1.6 g EPA + 800 mg DHA	4 g safflower oil	NC	NC	6wk	Increase in FFM and reduction in BF in ω-3 group.
Gravina et al.	2017	Clinical Trial	26 (19/7)	0.1 of ω-3/kg/day	0.1 of placebo/kg/day	3-d weighed food diary	Training diary		Only ω-3 group improved in a test of anaerobic endurance capacity (Yo-Yo test)
Harden et al.	2014	RCT, double-blind, controlled	27 (0/27)	2.8 g DHA	2.8 g oleic acid	3-d food diary	NC	12wk	No change in LM.
Hayward et al.	2016	RCT, open label, controlled	28 (0/28)	60 g whey protein +540 mg EPA + 360 mg DHA or 60 g whey protein + ω-3 + 5 g creatine	One group only in RT	7-d diary	RT 3x/wk	9wk	No beneficial effects on LM gains for ω-3 supplementation.
Hill et al.	2007	RCT, double-blind, controlled	68 (24/44)	1.56 g DHA + 360 mg EPA	6 g safflower oil	Weighted food record	AT 3x/wk	12wk	No differences were observed on LM across all groups

Notes: RCT = randomized clinical trial; m = men; w = women; NA = not applicable; CLA = conjugated linoleic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; wk = weeks; mo = months; NC = not controlled; RT = resistance training; AT = aerobic training; MPS = muscle protein synthesis; FFM = fat free mass; BF = body fat; LM = lean body mass; TUG = time up and go test; HGS = handgrip strength; 1-RM = one repetition maximum.

Adequate intake and/or supplementation of ω-3 has been associated with better control of lipid profile [14,15], decreased inflammation [16], attenuation of metabolic syndrome [17]; and reduced risk of coronary heart disease, ischemic stroke, and sudden cardiac death [18,19], although these findings remain equivocal [20,21]. Recently, ω-3 has been studied as a possible nutritional intervention to promote muscle mass and strength gains [22–27]. Some studies report positive effects of ω-3 intake on muscle mass and physical function [24–27], and these benefits are shown to occur in both young [24] and older [25–27] individuals, but this is not a consensus [22,23]. Low muscle mass and strength are associated with an impairment in walking [28], increased risk of falls [29] and higher mortality [30–32]. Therefore, nutritional strategies, such as consumption of ω-3, aiming to increase or maintain muscle mass and physical function are important, regardless of age. Thus, the aim of this narrative review was to evaluate the current evidence of ω-3 intake/supplementation on muscle/lean mass (LM) and physical function in young and older adults, and draw research-based conclusions as to the practical implications of findings. We first assessed whether ω-3 intake is associated with muscle mass and strength (observational studies), and then sought to determine whether evidence shows that supplementation of ω-3 increases muscle protein synthesis, LM and strength in adults and older adults (interventional studies).

2. Evidence from observational studies

In a cross-sectional and retrospective cohort study with 1519 men and 1414 women, Robinson et al. [25] found that fatty fish intake was the largest predictor of muscle strength (handgrip strength - HGS) both in men and women. Each additional portion of fatty fish consumed per week resulted in a 0.48 kg (95% CI 0.24 to 0.72) increase in HGS in women, and a 0.43 kg (95% CI 0.13 to 0.74) increase in men, whereas the consumption of white fish and shellfish did not correlate with HGS. Although the authors did not evaluate actual ω-3 intake, findings suggest that ω-3 may at least partially explain this association, since fatty fish intake is a primary source of this PUFA.

Several studies have investigated the association of ω-3 content in red blood cells or in the plasma (that may reflect the dietary pattern of ω-3 [33]) with muscle mass, strength and functional capacity [34–37]. Belury et al. (2016) did not find an association between ω-3 fatty acids composition in erythrocyte and LM in older adults [34]. Another study [35] investigated the association of plasma PUFA, including ω-3, with muscle size and strength in older adults at baseline and after 5 years of follow-up. Muscle size was not associated with total ω-3 PUFAs, ALA, DHA and EPA at baseline and over 5 years of follow-up. Total ω-3 PUFAs, DHA and EPA were positively associated with HGS at baseline; however, the associations were no longer significant after adjustments for confounding variables and no associations were found in longitudinal analysis. Alternatively, the longitudinal data showed that ALA was positively associated with increased knee extension strength.

Recently, it was observed that older adults with a lower percentage of total ω-3 fatty acid content in red cells presented reduced physical function; however, after adjustments for confounders, the association disappeared [36]. In a subsequent longitudinal study carried out over a 3-year period, the same research group evaluated the association between ω-3 fatty acid content in red cells and physical performance [37]. The authors' found that the individuals with lower ω-3 levels had lower gait speed in unadjusted model, but the significance was lost after adjustments for confounders. In addition, no association was found between ω-3 levels and short physical performance battery [37]. However, the study was limited by the fact that plasma ω-3 fatty acid content in red cell was assessed only at baseline, and hence this concentration may have changed over the follow-up period via food intake fluctuations. Multiple measurements of ω-3 in red cells at regimented intervals over time would be needed to more fully investigate the association between plasma PUFA and muscle/function parameters; this gap in the literature should be explored in future studies.

In summary, cross-sectional studies do not seem to show that ω-3 is associated with muscle mass, but some studies indicate a possible association between ω-3 and muscle function. However, these associations seem to be indirect, since the relationship between variables disappeared after statistical adjustments in the majority of the studies. Limited longitudinal data show that ω-3 intake is not associated with muscle size and some muscle function parameters, such as grip strength and gait speed; but it is likely associated with knee extension strength. It is important to note that these studies were carried out in older adults and associations in young adults remain to be elucidated. Moreover, observational studies are inherently limited because they do not afford the ability to draw causality.

3. Ω-3 and muscle protein synthesis

An important determinant of muscle loss with aging seems to be a decrease in muscle protein synthesis (MPS) [38], with older adults presenting lower MPS rates compared to young individuals with the same nutritional anabolic stimulus [39,40]. Thus, nutritional interventions aiming to increase MPS potentially can be important for muscle loss prevention [41].

The exact mechanisms by which ω-3 could mediate an increase in MPS remain unknown, but may be involved with alterations in catabolic and anabolic pathways. It is known that ω-3 is incorporated into cellular membranes of various body tissues, including skeletal muscle [5], modulating lipid–protein interactions. This incorporation seems to be a chronic process that can be observed after just 2 weeks of supplementation [33]. In muscle cells (myocytes), EPA and DHA, may enhance membrane fluidity, improving the uptake of amino acids and, consequently, making the cell more sensitive to MPS [42–45]. However, studies evaluating ω-3 supplementation and MPS have shown contradictory results; some studies found improvements in MPS and in anabolic response [43,44], while others showed no increase in MPS [5] or even an impairment in anabolic signaling [42].

3.1. Ω-3 and protein synthesis in young adults

Smith et al. [43] investigated the effect of ω-3 supplementation (1.86 g of EPA and 1.5 g of DHA) on MPS in 9 middle aged adults over an 8 week study period. Insulin and amino acid infusion was obtained at baseline and after 8 weeks of ω-3 supplementation, with results showing supplementation-induced pre-to post-study increases in Akt^{Thr308}, mTOR, p70s6k and MPS, translating into a ~50% greater anabolic response. However, the absence of a control group may limit the interpretation of these data.

Recently, McGlory et al. [42] evaluated the effect of 5 g/day of FO (3.5 g EPA and 0.9 g DHA) or coconut oil on MPS and the activity of kinases involved in anabolic signaling. After 8 weeks of supplementation, the individuals performed an acute bout of unilateral resistance exercise followed by the intake of 30 g of whey protein. MPS increased similarly between conditions post-exercise. However, the activity of p70S6K1 was elevated 3h after the resistance exercise following protein ingestion only in the coconut oil group. Interestingly, despite the apparent attenuation in anabolic signaling, there was no detrimental effect on MPS in the FO group. The contradictory findings between these studies may be explained by differences in methodologies, such as the studied population (untrained vs. resistance trained) and the mode of amino acid administration (oral vs. intravenous). While the provision of amino

Table 2
Studies assessing the effects of ω-3 on muscle protein synthesis (MPS), lean/fat-free mass and muscle function in older adults.

Author	Year	Study design	n (m/w)	Intervention	Placebo	Diet	Exercise	Time	Main results
Observational studies									
Robinson et al.	2008	Cross-sectional and retrospective cohort	2933 (1519/1414)	NA	NA	FFQ	NC	NA	Fatty fish was the largest predictor of HGS in men and women.
Reinders et al.	2013	Cross-sectional/Longitudinal	836 (348/488) 459 (210/249)	NA	NA	FFQ	Self-reported	5y	Muscle size and HGS were not associated with total ω-3 PUFAs, ALA, DHA and EPA at baseline and over 5 years of follow-up. The longitudinal data showed that ALA was positively associated with increased knee extension strength.
Belury et al.	2016	Cross-sectional (baseline data from two crossover studies)	139 (40/99)	NA	NA	Fatty acid content at red blood cell membrane	Questionnaire not identified	NA	No association between ω-3 content at red blood cell membrane and LM.
Fougère et al.	2017	Longitudinal	400 (128/272)	NA	NA	ω-3 content at red blood cell membrane	NC	3 y	Individuals with lower ω-3 levels had lower gait speed in unadjusted model, but the significance was lost after adjustments for confounders
Fougère et al.	2017	Cross-sectional	1449 (515/934)	NA	NA	ω-3 content at red blood cell membrane	NC	NA	Individuals with a lower percentage of total ω-3 fatty acid content in red cells presented reduced physical function; however, after adjustments for confounders, the association disappeared
Interventional studies									
Sneddon et al.	2008	Crossover, double-blind, placebo-controlled	59 (59/0)	2.28 g CLA + 900 mg EPA + 630 mg DHA	4.8 g palm oil + 1.2 g soya bean oil	NC	NC	12wk	No changes were observed in muscle mass and fat-free mass.
Smith et al.	2011	RCT, double-blind, controlled	16 (10/6)	1.86 g EPA + 1.5 g DHA	4 g corn oil	NC	NC	8wk	FO enhanced the rate of MPS as well as increasing activation of mTOR and p70s6k concentration, although no change in Akt^{Thr308} was observed.
Lalia et al.	2017	Clinical trial, open-label	12 (5/7)	2.7 g EPA + 1.2 mg DHA	NC	NC	1 acute session	16wk	ω-3 supplementation increased postabsorptive muscle protein synthesis and enhanced anabolic responses to exercise
Hutchins-Wiese et al.	2013	RCT, double-blind, controlled	124 (0/124)	720 mg EPA + 480 mg DHA	1.8 g olive oil	2 food recall	NC	6mo	Improvements in walking speed in ω-3 group
Smith et al.	2015	RCT, double-blind, controlled	44 (15/29)	1.86 g EPA + 1.5 g DHA	4 g corn oil	NC	NC	6mo	Increases in thigh muscle volume, HGS, and 1-RM in ω-3 therapy compared to control group.
Logan and Spriet	2015	RCT, single-blind, controlled	24 (0/24)	2 g EPA +1 g DHA	3 g olive oil)	3 food recall	PASE Questionaire	12wk	ω-3 group increased LM and improved functional capacity
Strandberg et al.	2015	RCT, open label, controlled	55 (0/55)	Healthy diet (ω-6/ω-3 ratio < 2)	NC (control group maintaining their nutritional habits)	6-day food record 3 times	RT 2x/wk	24wk	Only the RT plus healthy diet group demonstrated an increase in leg LM
Edholm; Strandbergand Kadi, 2017	2017	RCT, open label, controlled	63 (0/63)	Healthy diet (ω-6/ω-3 ratio < 2	NC (control group maintaining their nutritional habits)	6-day food record 3 times	RT 2x/wk	24wk	RT plus healthy diet group presented significant improvements in dynamic explosive capacity during isolated lower limb movements and multijointed exercises.
da Boit et al.	2017	RCT, double-blind, controlled	50 (27/23)	2.1 g EPA + 600 mg DHA	3 g of safflower oil	NC	RT 2x/wk	18wk	Women showed an increase in maximal isometric torque and muscle quality in ω-3 group, with no changes in placebo

									group after exercise training. No changes in MPS or muscle mass.
Rodacki et al.	2012	RCT, open label, controlled	45 (0/45)	0.8 g EPA + 0.6 of DHA	NC (RT alone)	FFQ	RT 3x/wk	12wk	FO supplementation improved peak torque, muscle activation level, and chair-rising test.
Krzymińska-Siemaszko et al.	2015	RCT, open label, controlled	50 (17/33)	660 mg EPA + 440 mg DHA + 200 mg other ω-3 + 10 mg vitamin E	10 mg vitamin E	NC	NC	12wk	No changes in body composition and muscle function.
Tardivo et al.	2015	RCT, open label, controlled	63 (0/63)	540 mg EPA + 360 mg DHA	NC (Only diet)	3 food recall	NC	6mo	No changes in muscle mass
Cornish et al.	2018	Randomized, double-blind, controlled	23 (23/0)	1.98 g of EPA and 0.99 of DHA	alpha linolenic acid, linoleic acid and gamma linolenic acid, oleic acid	3-day food diary	RT 3x/wk	12wk	Supplementation with EPA and DHA had no ergogenic effect on the timed-up-and-go and 6-minute walk tests. Both groups similarly increased lean tissue mass
Cornish and Chilibeck	2009	RCT, double-blind, controlled	51 (28/23)	14 g ALA	30 ml of corn oil	FFQ	RT 3x/wk	12wk	Significant increases in LM and 1-RM strength were found in both groups with no differences observed between conditions

Notes: RCT = randomized clinical trial; m = men; w = women; NA = not applicable; CLA = conjugated linoleic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; y = years; wk = weeks; mo = months; FFQ = food frequency questionnaire; FO = fish oil; NC = not controlled; RT = resistance training; AT = aerobic training; MPS = muscle protein synthesis; FFM = fat free mass; BF = body fat; LM = lean body mass; TUG = time up and go test; HGS = handgrip strength; KES = knee extension strength; 1-RM = one repetition maximum.

acids by Smith et al. [43] was continuous (infusion), McGlory et al. [42] provided a bolus of whey, which is known to promote a peak of aminoacidemia (by ingestion) followed by a rapid decrease in blood levels. Another important difference to take into account is that Smith et al. [43] clamped the plasma when a leucine concentration of ~65–175 μmol/L was achieved, which would represent a sub-maximal dose, while peak of plasma leucine concentrations in McGlory et al. [42] were ~250–300 μmol/L, which equates to ~0.35 g of protein/kg; a value sufficient to maximize the rate of MPS in young men. Thus, it can be speculated that a greater amount of ω-3 in the cell appears to enhance anabolism when the dose of protein is insufficient to stimulate a maximum MPS response. However, when a maximal MPS response is achieved by protein stimulus, supplementation with ω-3 seems to promote no increase in MPS response to resistance training. This hypothesis is based on limited data and further research is needed to draw more concrete inferences.

3.2. Ω-3 and protein synthesis in older adults

Smith et al. [44] conducted a RCT with 16 older adults that compared the effect of FO supplementation (1.86 g of EPA and 1.5 g of DHA) versus placebo (4 g of corn oil) on MPS. After 8 weeks of supplementation, subjects underwent a hyperaminoacidemia-hyperinsulinemia clamp to assess the rate of MPS and phosphorylation of various anabolic signaling elements. Results showed that supplementation with FO enhanced the rate of MPS as well as increasing activation of mTOR and p70s6k concentration, although no change in Akt^{Thr308} was observed. Lalia et al. [46] also aimed to evaluate the influence of ω-3 supplementation on MPS and anabolic response to an acute exercise bout in healthy older adults. Twelve volunteers received 3.9 g/day of ω-3 (2.7 g EPA and 1.2 g of DHA) for 16-week in an open-label intervention. Small, non-significant increases in myofibrillar protein synthesis were noted in the pre-exercise post-absorptive state following 16 weeks of ω-3 supplementation; however, the rates of myofibrillar fractions were significantly higher after exercise. Intriguingly, the resistance training-induced increase in MPS following ω-3 supplementation was greater in older versus younger individuals.

Although there is a relative dearth of studies evaluating the effect of ω-3 supplementation on MPS in older adults, it seems that ω-3 can promote anabolic increases in these individuals. These findings persist despite heterogeneity in methodological designs, with an amino acid infusion employed in one study [44], and consumption of a mixed meal and an exercise bout in the other [46].

In summary, the current data shows promise for a beneficial anabolic effect of ω-3 in older adults, but further research is needed to draw stronger conclusions on the topic. Areas of interest include comparing the MPS response to ω-3 supplementation after different protein doses, both with and without exercise, as well as during bed rest conditions. Future studies are also needed to elucidate the effect of ω-3 supplementation on the attenuation of anabolic resistance in older adults.

4. Evidence from interventional studies

4.1. Ω-3 and muscle mass (without exercise)

4.1.1. Young adults

Although MPS is recognized as the primary driver of muscle hypertrophy [47], the acute MPS response does not always correlate with long-term muscle hypertrophy [48]. Thus, longitudinal studies are needed to determine whether ω-3 consumption promotes actual changes in muscle mass. One of the first studies on the topic

investigated the influence of FO on body composition in 6 adults, whereby participants initially ingested an ad libitum control diet for 3 weeks [49]. After a 10–12 weeks washout period, the participants ingested an ad libitum diet over a 3-week period with the substitution of 6 g/d of FO for an equal amount of other dietary lipids. No change in fat free mass (FFM) was found for either condition, although FO group presented a higher decrease in body fat. These results should be interpreted with caution due to the small sample size, absence of a parallel control group, and short study duration. In agreement with these results, Harden et al. [22] investigated the effect of supplementation of DHA (2.8 g/day) or oleic acid (olive oil) on body composition in obese women. The study employed double-blinded, 2-way, parallel design, with no differences reported in LM between conditions following the 12-week intervention. It should be noted that the study by Harden et al. [22] is specific to consumption of DHA; there is evidence that EPA has differential biological effects from DHA [50], and it is not clear whether their combined intake promotes synergistic benefits.

However, other studies [24,51] found a possible effect of ω-3 supplementation on LM. Noreen et al. [24] carried out a double-blind study whereby 44 adults were randomly assigned into one of two groups: a placebo group that received 4 g/day of safflower oil, or group that received the same dose of FO (equating to 1.6 g of EPA and 800 mg of DHA). After the 6-week intervention period an increase in FFM and a decrease in fat mass were observed in the FO group, which were both statistically greater compared to the safflower oil supplement. Although these results are intriguing, they should be interpreted with circumspection as it would seem unlikely that an isolated nutritional intervention can promote a concomitant gain in LM and loss in fat mass in the absence of regimented resistance training, as shown in this study. Moreover, the absence of dietary control may have influenced the results. A possible explanation for the findings is the use of air displacement plethysmography for body composition analysis, which may have been unduly influenced by changes in hydration status. In a double-blind, placebo-controlled, crossover study [51], lean and obese young and older adults were submitted to 12 weeks of supplementation, followed by a washout period of the same duration. Subjects consumed either 6 capsules of conjugated linoleic acid (CLA; C18:2n-6) + ω-3 (2.28 g of CLA, 900 mg of EPA, and 630 mg of DHA) or 6 capsules of control (4.8 g of palm oil and 1.2 g of soya bean oil) per day. Results showed CLA + ω-3 treatment increased FFM (1.3%) in young obese men, but supplementation had no effect in lean young adults. The reasons for discrepancies between populations is not clear, but an important limitation is that the study did not directly control for food intake and physical activity levels. Moreover, the addition of CLA to the ω-3 treatment confounds the ability to draw causality with respect to the effects of EPA and DHA.

When evaluating the current evidence, it remains equivocal as to whether ω-3 supplementation enhances LM in young adults who do not perform exercise. Although some studies show modest increases in LM in this population, the lack of control for physical activity and dietary intake precludes the ability to draw inferences as to whether LM gains occurred due to ω-3 supplementation per se or to confounding factors.

4.1.2. Older adults

Several studies have endeavored to determine the long-term effects of ω-3 in older adults. In the study by Sneddon et al. [51] discussed above, the combination of CLA + ω-3 supplementation did not augment LM compared to oleic acid in both lean and obese older adults following a 12-week intervention period. Similarly, Krzymińska-Siemaszko et al. [52] randomized 50 older adults with low baseline muscle mass to either a PUFA-treated group (660 mg of EPA, 440 mg of DHA, 200 mg of other ω-3, plus 10 mg of vitamin E) or control (11 mg of vitamin E). After 12 weeks of supplementation, no changes were observed in muscle mass and fat-free mass. Lending further support to these findings, Tardivo et al. [53] found that changes in muscle mass were not significantly different in postmenopausal women receiving a dietary intervention plus ω-3 supplementation (3 capsules/day, each one containing 180 mg of EPA and 120 mg of DHA) versus a dietary intervention alone (control group) over a 6-month study period.

In contrast to the aforementioned studies, Logan et al. [26] randomized 24 community-dwelling older women into one of two groups: FO (5 g/day; 2 g of EPA and 1 g of DHA) or placebo (3 g/day of olive oil). Both groups were instructed to maintain their current physical exercise and dietary regimen. After 12 weeks of supplementation, an increase in LM (~4%) was noted in the FO group whereas no significant changes were found in placebo. In a double-blind, placebo-controlled trial, Smith et al. [54] randomly assigned a cohort of older men to receive either ω−3 supplementation (4 pills/day of 1.86 g EPA and 1.50 g of DHA) or placebo (4 pills/day of corn oil). At the end of the 6-month intervention period, results showed a significant increase in thigh muscle volume for subjects supplemented with ω−3, as determined by magnetic resonance imaging, widely considered the gold standard criterion.

In summary, the evidence is mixed as to the effects of ω−3 supplementation on muscle mass in older, sedentary individuals, with some studies demonstrating beneficial changes [26,54] and others failing to show a benefit [51–53]. The current literature is, in general, limited by a lack of control for dietary intake and physical activity levels. Moreover, many of the studies employed bioelectrical impedance analysis to measure FFM, which may lack the accuracy to detect subtle changes in this parameter over relatively short time frames.

4.2. Ω-3 and muscle mass (with exercise)

4.2.1. Young adults

To the best of our knowledge, only two studies have endeavored to investigate the combined effects of ω-3 supplementation and physical training on body composition changes in young individuals. Hill et al. [55] conducted a 12-week double-blind RCT whereby young adults were allocated into 4 groups. Two groups performed aerobic exercise (running or walking, 3 times per week, 45 min, at a heart rate of 75% of their age-predicted maximum). One of these groups received capsules containing FO (1.56 g of DHA and 360 mg of EPA), while the other received placebo (6 g of sunflower oil). The two groups that did not perform aerobic exercise also received the same supplementation protocol (treatment or placebo). Although the FO plus exercise group showed a greater decrease in body fat, no differences were observed on LM across all groups. The lack of change in LM could be expected since steady-state aerobic exercise protocols have minimal hypertrophic effects.

More recently, Hayward et al. [56] randomized 28 healthy untrained young females into one of three groups, all of whom performed a supervised resistance exercise protocol: 1) control (only exercise); 2) higher-protein diet plus ω-3; and 3) higher-protein diet plus ω-3 plus creatine monohydrate. The study protocol lasted 8 weeks, with 4 weeks devoted to pre-training and 4-weeks of resistance training plus dietary intervention. Results showed no beneficial effects on LM gains for ω-3 supplementation.

The limited data to date does not support a hypertrophic benefit for ω-3 supplementation when combined with structured exercise in young adults. However, conclusions must be interpreted with caution as one study [55] employed low-intensity aerobic exercise (walking), which would not be expected to promote LM gains; and the other study that did employ resistance training [56] involved only 4 weeks of ω-3 supplementation, which may not be of

sufficient duration to observe a full incorporation of n-3 PUFA into membrane cells [57] and consequently increase biological function. Clearly, more studies are needed to elucidate whether ω-3 supplementation enhances the accretion of LM/muscle mass in exercising young adults.

4.2.2. Older adults

Several studies have investigated the effect of ω-3 supplementation in combination with exercise on muscle mass in older adults. Cornish et al. [23] randomized 51 older men and women to receive a supplement consisting of either 30 g of corn oil (placebo) or flaxseed oil (~14 g of ALA) for 12 weeks. All subjects performed a periodized total-body RT program 3 times per week. Significant increases in LM were found in both groups with no differences observed between conditions.

Similarly, Da Boit [5] failed to demonstrate a beneficial effect of ω-3 (3 g fish oil/d) on muscle mass compared to placebo (3 g safflower oil/d) in older men and women performing resistance training twice weekly for 18 weeks. Curiously, none of the groups significantly increased muscle cross sectional area following the lengthy study period. These findings run contrary to the compelling body of literature, which shows that older individuals achieve robust gains in markers of muscle mass from structured resistance training [58]. This raises questions as to whether the program was sufficiently challenging to bring about hypertrophic adaptations. In addition, the analysis of quadriceps muscle anatomical cross-sectional area was performed on only 5 slices (the midpoint slice and 2 slices immediately inferior and superior to the midpoint); it therefore is possible that non-uniform changes between conditions may have occurred across the muscle that went undetected by the employed methodology.

Most recently, Cornish et al. [59] carried out a double-blind study, whereby 23 older men were randomly assigned to consume either 3.0 g of a combined EPA/DHA supplement (1.98 g of EPA and 0.99 g of DHA) or an equal amount of an omega fatty acid blend containing alpha linolenic acid (1.35 g), linoleic acid and gamma linolenic acid (0.795 g), oleic acid (0.525 g). Both groups completed a 12-week total body resistance training program carried out on 3 nonconsecutive days per week. Post-study results showed that both groups similarly increased lean tissue mass as measured by dual x-ray absorptiometry. A possible confounding issue is that the relatively high alpha linolenic acid content (45%) in the control supplement may have unduly influenced findings.

In contrast to the aforementioned null findings, Strandberg et al. [27] conducted a three-armed RCT in older women that included a diet and resistance exercise intervention. Subjects were randomly allocated to either control, RT, or RT plus a healthy diet with ω-6/ω-3 ratio <2. The control and RT groups were advised to maintain their nutritional habits, whereas the RT plus healthy diet increased their ω-3, PUFA and MUFA intakes and decreased their saturated fat and ω-6 intakes. At the end of the 24-week intervention, only the RT plus healthy diet group demonstrated an increase in leg LM (~2%). It should be noted that the study did not aim to evaluate the effect of ω-3 supplementation alone, as the ratio of other fats were altered as well. Therefore, it is only possible to conclude that a "healthier" fat intake, which includes an increase of ω-3 intake, promoted benefits for older individuals involved in resistance exercise.

In a follow up study from the same lab, Strandberg et al. [60] randomized recreationally active older women to one of three groups: resistance training and ω-3 rich diet; resistance training only; or controls. Increased ω-3 intake was achieved by consumption of ≥500 g/wk of fatty fish including salmon, mackerel, and herring. Subjects realized resistance training twice a week with exercises for all the major muscle groups. After 24 weeks, only the group consuming higher amounts of ω-3 significantly increased type 2 fiber hypertrophy as determined by muscle biopsy. As with their previous study, the ratio of other dietary fats was altered in the nutritional prescription, which in turn confounds the ability to draw causality as to the specific effects of ω-3 alone on muscular gains.

In sum, the literature remains equivocal as to whether ω-3 supplementation enhances increases in LM/muscle mass when consumed in conjunction with a regimented resistance exercise program. Further research is needed in this area to draw relevant inferences.

4.3. Ω-3 and physical function

The mechanisms that explain the improvement in physical function remain to be fully elucidated, but it has been speculated that ω-3 may promote benefits on this outcome by increasing acetylcholine sensitivity and membrane fluidity [61]. Acetylcholine is a neurotransmitter that supports muscle contraction, making synaptic transmission faster at the neuromuscular junction and thus resulting in a faster contractility [61]. With respect to the cellular membrane, there may be an effect on endocytosis, exocytosis, membrane fusion, and neurotransmitter uptake and release [62]. Given that neuronal function declines with ageing, ω-3 can be an important interventional strategy for staving off these detrimental effects [26]. Considering the logical rationale for a potential benefit of ω-3 on muscle function, the following sections look at the evidence from interventional studies on the topic to determine if there is actual efficacy for supplementation.

4.3.1. Young adults (without exercise intervention)

Only one study to date investigated the effect of ω-3 supplementation on physical performance in young individuals [63]. Competitive soccer players were randomized into a group that supplemented with ω-3 (70% of EPA, 20% of DHA and 0.02 mg of vitamin E per gram) or placebo (7% of caprylic acid, 92% of capric acid, 0,9% of lauric acid, and 0.3% of palmitic acid). Although the study did not employ a specific exercise intervention, training session intensity, competitive games, and nutritional intake were monitored. After 4 weeks of supplementation, only the ω-3 group improved in a test of anaerobic endurance capacity (i.e. the Yo-Yo test). Although the study's objective was to evaluate the effect of ω-3 supplementation on physical function, a controlled exercise intervention together with the supplementation was not performed.

4.3.2. Older adults (without exercise intervention)

Several studies have sought to investigate the effect of ω-3 supplementation on physical function without exercise intervention in older adults. Hutchins-Wiese et al. [64] randomly assigned 118 postmenopausal women to supplement with either FO (720 mg of EPA and 480 mg of DHA) or placebo (1.8 g of olive oil) for 6 months. Post-study evaluation of physical function revealed significant improvements in walking speed for the FO group compared to placebo. The previously mentioned study by Logan and Spriet [26] found that 12 weeks of FO supplementation improved functional capacity by 7%, while no changes were observed in placebo group; and another study [54] reported an increase in handgrip strength and 1-RM following 6 months of ω-3 supplementation, despite the absence of a regimented exercise intervention. It is important to note that neither study [26,54] attempted to control subjects' physical activity levels during the intervention, which may have confounded results.

Based on limited data, the evidence shows that ω-3 supplementation may help to enhance muscle function in older adults,

even without an exercise component. More research is needed with better control of physical activity and dietary intake to confirm these conclusions.

4.4. Ω-3 and physical function (with exercise)

4.4.1. Young adults

To the best of our knowledge, only one study [56] investigated the effect of ω-3 supplementation on the physical function of young adults who performed an exercise intervention. Participants were randomized into three groups that performed regimented resistance exercise: 1) control (only exercise); 2) higher-protein diet plus ω-3; and 3) higher-protein diet plus ω-3 plus creatine monohydrate for 4 weeks of supplementation. All groups showed an increase in 1-RM strength for the bench press, squat, deadlift, and hip thruster, with no differences between the interventions. This isolated finding indicates that the ω-3 supplementation does not promote greater gains in muscle strength during resistance training, although additional research is needed to better evaluate the effect of ω-3 supplementation on physical function in young adults.

4.4.2. Older adults

Cornish et al. [23] compared the effect of 30 g of corn oil (placebo) or flaxseed oil (~14 g of ALA) for 12-weeks in individuals who performed RT three times per week. Both groups increased 1-RM strength, with no additional effects in the ALA group. Contrary to these findings, Rodacki et al. [65] randomly allocated 45 older women to one of three groups: RT alone, RT + FO for 90 days, or RT + FO for 150 days (supplementation began after day 60). The FO groups received two capsules of FO (containing 0.8 g of EPA and 0.6 g of DHA) per day. Training comprised 3 sets of 8 repetitions of multiple exercises for the lower limbs performed 3 times per week. Participants were instructed to maintain their usual diet and physical activity levels, and had their eating habits evaluated by FFQ. At study's end, all groups increased their muscle function; however, both FO groups realized greater improvements in muscle strength and functional capacity. Importantly, the absence of a placebo group is a limitation of this study, since a placebo effect can occur for muscle function improvements.

Recently, da Boit et al. [5] evaluated the effect of ω-3 (3 g fish oil/d) or placebo (3 g safflower oil/d) plus lower-limb resistance exercise training carried out twice per week for 18 weeks in older men and women. Women who supplemented with ω-3 showed greater improvements in maximal isometric torque and in muscle quality (strength per unit of muscle area). However, no beneficial effects on muscle function were observed in men after ω-3 supplementation. These sex-related differences may have be occurred because older women do not seem to increase muscle strength to the same magnitude as older men [66]; however, this is highly speculative since other research [67] failed to observe differences in strength gains between sexes.

The possible improvements in muscle function induced by ω-3 supplementation were also observed by a recent study [68]. Three groups were compared: control, RT, and RT plus a healthy diet high in ω-3 on muscle function, similar to the previous design employed by previous study performed by the same laboratory [27]. Results showed greater improvements in dynamic explosive capacity during isolated lower limb movements and multijoint exercises in the group consuming high intakes of ω-3 and MUFA and lower amounts of saturated fat and ω-6 compared to the group that only performed RT without any dietary modifications. Alternatively, the recent study by Cornish et al. [59] found that supplementation with EPA and DHA had no ergogenic effect on the timed-up-and-go and 6-minute walk tests following 12 weeks of regimented resistance exercise.

Collectively, the evidence remains conflicting as to whether ω-3 supplementation promotes greater improvements in muscle function induced by resistance exercise in older adults. This conclusion is based on somewhat limited data and more studies are needed to elucidate potential nuances and mechanisms of action.

5. Potential limitations of the current studies and suggestions for the future

We should highlight that a large number of studies included in this review did not control for food intake and physical activity levels. This confounds the ability to draw causality as to the effect of ω-3 on body composition and/or muscle function. It is important to control nutritional intake during studies focused on muscular adaptations, and particularly protein consumption, since it influences the accretion of muscle mass and physical function. Moreover, it is well-established that exercise is a primary modulator of muscle mass [69], and thus controlling physical activity levels is paramount in this regard.

The use of ω-3 supplements may cause adverse effects in gastrointestinal tract and few studies reported this information. The "fish taste" after the consumption of the supplement may characterize the study as open-label. Thus, any difference in taste, smell, mode of administration or appearance could interfere with blinding [70].

Another limitation for comparing results among studies is the high variability of the placebo provision, which includespalm oil, soya bean oil, corn oil, olive oil, coconut oil, safflower oil and ALA. Moreover, other studies compared the effects of ω-3 supplementation with a control group that had no placebo provision. Therefore, standardization of the placebo used in future studies can help to conclude the true effect of ω-3 supplementation on muscle mass and strength, since differences in placebo content can promote differential changes in fatty acid incorporations into cell membrane.

In addition, many of the studies evaluated changes in muscle mass/LM by bioimpedance, which may not have the precision to detect subtle increases in muscle mass over short-term interventions. Thus, more studies using more accurate body composition methodologies are needed to detect changes in LM or muscle, such as CT or MRI. However, even when MRI is used, a better standardization in methodology is needed for more accurate comparison.

Therefore, these factors highlight the importance of adequate assessment of dietary intake and physical activity in future studies, as well as the correct blinding and use of gold standard methods of body composition.

6. Conclusions

The observational studies do not show significant associations between ω-3 intake and muscle mass. The associations between ω-3 intake and muscle function do not seem to be significant after adjustments for confounders, with exception of one observational study (longitudinal design) that showed that ALA was associated with knee extension strength (Fig. 1). Thus, the clinical relevance of the association between ω-3 intake and muscle function is questionable. Importantly, these studies are relegated to older individuals and thus cannot be generalized to young adults.

In addition, the evidence is mixed as to the effects of ω−3 supplementation on muscle mass in sedentary young and older adults; the hypertrophic effects of supplementation when combined with resistance training remain equivocal. Moreover, there is

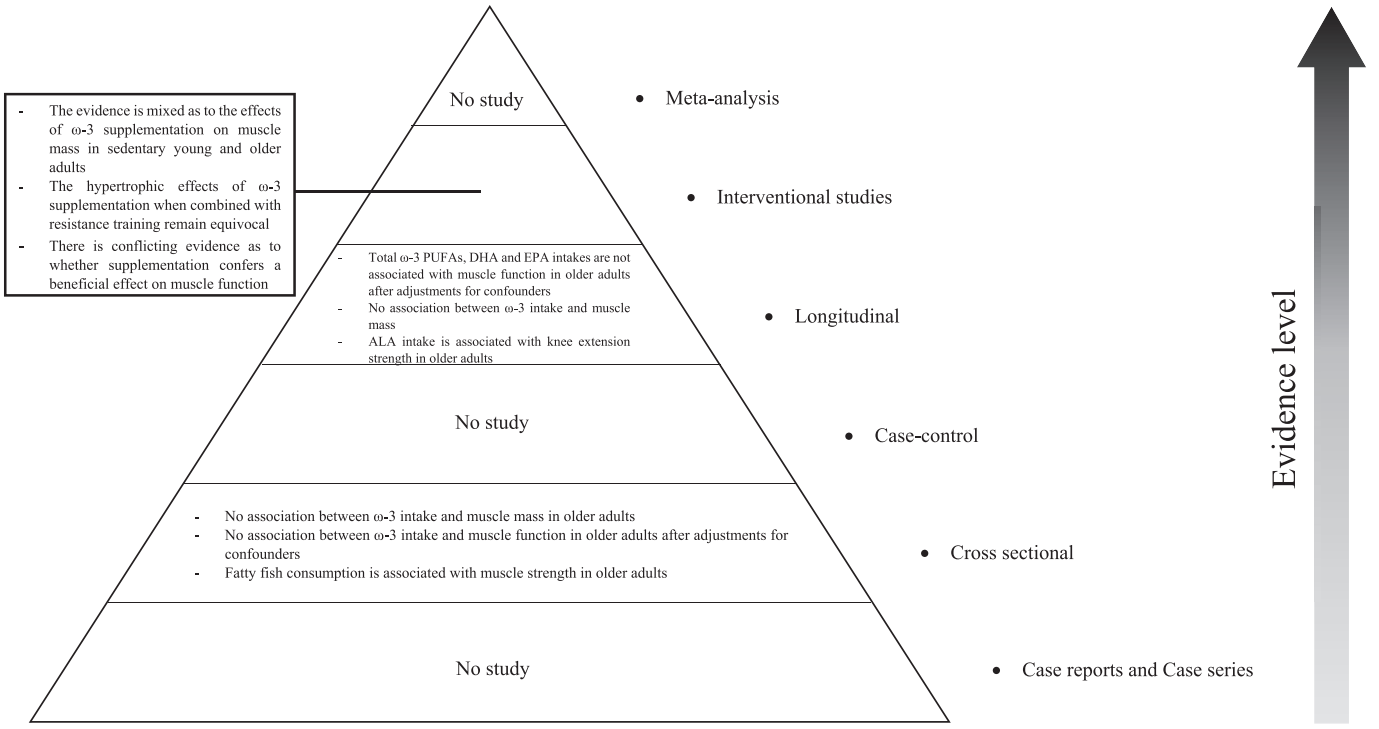

Fig. 1. Scientific evidence to supplement omega-3 fatty acids to increase muscle mass and strength in young and older adults.

conflicting evidence as to whether supplementation confers a beneficial effect on muscle function in older adults (Fig. 1). Importantly, this conclusion is based on limited data and more studies are needed before ω-3 supplementation can be recommended as a viable strategy for such purposes in clinical practice.

Conflicts of interest

LTR and EPO declare no conflicts of interest. BJS serves on the advisory board to Dymatize Nutrition, and has received funding from the company for studies unrelated to ω-3.

Authorship

LTR, BJS and EPO participated in the writing and critical revision of the article. All authors read and approved the manuscript.

Funding

No sources of funding were used to assist in the preparation of this article.

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