Fish oil derived n-3 polyunsaturated fatty acids for the prevention and treatment of sarcopenia

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Abstract

Purpose of review: Muscle mass and function decline progressively starting in middle age, which can result in sarcopenia and affect people's mobility and independence late in life. Exercise training and increased protein intake are typically recommended to counteract the age-associated decline in muscle mass and function. However, few people comply with exercise recommendations and evidence for the anti-sarcopenic effectiveness of high protein intake is lacking. This review aims to explore recent developments in the potential for fish-oil derived n-3 polyunsaturated fatty acids (n-3 PUFA) to improve muscle mass and function in older people.

Recent findings: The results from recent studies demonstrate that dietary supplementation with fish oil-derived n-3 PUFA stimulates muscle protein synthesis and improves muscle mass and function in sedentary older adults and augments the resistance exercise training-induced increase in muscle strength. The exact mechanisms by which fish oil-derived n-3 PUFAs exert their beneficial effects on muscle mass and function remain to be elucidated.

Summary and Conclusion: Fish-oil supplementation has anti-sarcopenic effects and should be considered in the clinical care of older adults.

Keywords: Sarcopenia, weakness, frailty, omega-3 fatty acids

Introduction

Starting in late middle-age, skeletal muscles atrophy progressively and muscle tissue undergoes morphological changes (e.g., infiltration with non-contractile material, such as fat and connective tissue; reduced capillary density and mitochondrial content; motor unit and neuromuscular junction remodelling) which can reduce muscles' ability to generate and maintain force, and negatively affect activities of daily living (walking, climbing stairs, lifting items) [1-3]. In healthy people muscle mass and strength decline by ~0.5%-1.0% and 1%-2% per decade, respectively; periods of acute illness and chronic diseases accelerate these processes. A decrease in muscle mass and physical abilities (walking speed and/or strength) below certain threshold values, established by the *International Sarcopenia Initiative* [1], is referred to as sarcopenia. Sarcopenia is associated with a 2-3-fold increased risk of falls (~20% increase in incidence for each ~15% decrease in leg strength), frailty, disability, loss of independence, and mortality (~4% increase for every 1 kg decrease in grip strength) [1, 4-9]. Sarcopenia affects 10-30% of independently living older adults, without major illness, and even more ill and/or institutionalized older adults [1, 10-12]. The total number of people affected by sarcopenia is expected to rise significantly because, according to U.S. Census Bureau Population Projections (www.agingstats.gov), the number of older adults (>65 years of age) is expected to double in 25 years, until the youngest Baby Boomers" reach 65 years of age. No safe and effective drug therapies for the prevention and treatment of sarcopenia exist. Current recommendations, therefore, focus on exercise training and high protein intake, but these approaches have limitations as outlined below. Fish oil-derived n-3 polyunsaturated fatty acids (n-3 PUFA) (eicosapentaenoic and docosahexaenoic acid) have emerged as a potential new treatment modality for the prevention and treatment of sarcopenia that warrant serious consideration in the clinical care for older adults.

Physical activity and the risk of sarcopenia

Regular physical activity, particularly resistance type exercise, is the cornerstone for maintaining adequate muscle mass and function throughout life [1, 13-15]. However, even life-long exercisers and highly trained master class athletes exhibit a progressive loss of muscle mass and function [16-18]. Moreover, a plethora of health-, environment-, and self-related factors represent barriers to initiate and continue exercise programs in the general population [19-22]. Indeed, only 10% of older adults engage in physical activities that enhance and maintain strength and endurance on two or more days per week and only 15-20% make trips of one mile or less by walking [19, 23]. Muscle is very sensitive to disuse, and even short-periods of reduced use can have detrimental consequences in older adults because of the resulting loss of muscle mass (~5-8% after only 1-2 weeks of reduced ambulation) and function (~10% decrease in strength after only 4 days of immobilization) which are difficult to recover even with intense physical rehabilitation [24-26]. Accordingly, dietary changes are also recommended to mitigate the age-associated loss of muscle mass and function.

Current dietary recommendations to mitigate the risk and consequences of sarcopenia

International expert groups recommend a minimum protein intake of 1.0-1.2 g per kg body weight per day (which is 25%-50% more than the RDA of 0.8 g/kg/d) for healthy older adults, 1.2-1.5 g/kg/d for those who have acute or chronic diseases, and up to 2.0 g/kg/d during periods of acute illness [14, 15]. However, conclusive evidence that high protein intake has meaningful effects on muscle mass and/or function is lacking [27-33]. This may in part be due to the short duration of many of the studies which have evaluated the effect of protein intake on muscle mass and strength, but also because most studies paid little attention to participants' habitual protein intake, the source of protein and the timing of protein intake. High intake of leucine-rich proteins, such as whey protein, evenly distributed across meals is suggested to be particularly beneficial because protein ingestion stimulates muscle protein synthesis acutely in a dose

dependent manner and leucine supplementation augments the anabolic response to protein ingestion [15, 34-41]. Indeed, in one trial, it was found that adding 15 g milk protein to both breakfast and lunch, for 24 weeks, improved the Short Physical Performance Battery score [42]. Additional long-term high quality clinical trials are clearly needed in this area. On top of this, there are potential downsides to increasing protein intake to consider. The results from several small cross-sectional and large population studies have shown a link between high protein consumption and the development of insulin resistance and T2D [43-50]. The risk of developing T2D increases by 20-40% for every 10 g of protein consumed, in excess of 64 g/d, and the risk of developing T2D in people in the highest quartile of protein consumption is nearly twice that of those in the lowest quartile [47-49]. The potential adverse effect of high protein intake on the pathophysiological mechanisms underlying T2D has also been demonstrated in small randomized-controlled studies [51-55]. It is worth pointing out, however, that the authors of several recent systematic reviews and meta-analyses [56-59] have concluded that the available data are inadequate to determine the effect of high protein intake *per se* on insulin sensitivity and plasma glucose concentration, because of potential confounding influences of food selection and overall diet composition, differences between intervention and control groups, and the short duration of most trials.

Fish-oil derived n-3 PUFA – a potential new treatment modality to reverse sarcopenia

The results from epidemiological studies [60] and experiments in cell cultures and animals [61] suggest that fish oil-derived n-3 PUFA could have therapeutic effects in older adults. We [62] and another group of investigators [63] found that healthy, older women who participated in an exercise training program and consumed 2-4 g fish oil per day for 3 months had greater training-induced gains in muscle strength than those who did not supplement their diet with fish oil. We also found 6 months of dietary supplementation with 4 g of fish oil-derived n-3 PUFA, increased muscle mass and strength in healthy, physically active, but untrained older adults [64]. Daily

supplementation with 1.3 g of n-3 PUFA for 12 weeks, on the other hand, was not associated with improved muscle strength and global physical function in older adults [65]. The lack of an effect in this study was most likely due to both the low dose and short duration of the intervention, because we found significant increases in muscle mass and function after six but not three months of treatment with 4 g of fish oil-derived n-3 PUFA per day [64]. Unlike high protein intake, there is no evidence that these fatty acids have any adverse effects on cardiometabolic health [66-69], which supports their use in older adults who are most susceptible to cardiometabolic disease.

The mechanisms responsible for the beneficial effects of fish oil-derived n-3 PUFAs on muscle mass and function have not been fully elucidated, but are likely multifactorial including several, or all of the ones outlined in **Figure 1**. Changes in muscle mass result from changes in both protein turnover (balance between synthesis and breakdown) and cell turnover (balance between satellite cell proliferation and fusion and myonuclear loss). We found that adding 4 g of fish oil-derived n-3 PUFA per day for 8 weeks to the diet of healthy older adults increased the acute amino acid induced activation of the mTOR-p70s6k signalling pathway and muscle protein synthesis [70]. Others found that adding 3.9 g of fish oil-derived n-3 PUFA to the diet of older adults augmented the acute exercise-induced increase in muscle protein synthesis [71]. The effect of fish oil-derived n-3 PUFAs on muscle protein synthesis has also been investigated in young adults and the results are equivocal. We found that 8 weeks of fish oil-derived n-3 PUFA intake (4 g per d) increased the rate of muscle protein synthesis during amino acid and insulin infusion in sedentary young adults [72]. On the other hand, others found no effect of 8 weeks of fish oil-derived n-3 PUFA intake (5 g per d) on the rate of muscle protein synthesis in resistance trained young men, who consumed 30 g of protein at rest or after a bout of resistance exercise [73]. This was likely because the high protein intake combined with regular exercise training already maximally stimulated muscle protein synthesis in this participant group

[38]. Studies conducted in cell cultures, rats, and patients on maintenance hemodialysis found fish oil-derived n-3 PUFA also attenuated muscle protein breakdown [61]. The effect of fish oil-derived n-3 PUFAs on muscle cell turnover is not known.

Increased muscle function (strength and endurance) could be due to changes in myocytes themselves (myofiber microstructure, contractility, and energy production), as well as changes in external factors (extracellular matrix composition and function, muscle perfusion, and neuromuscular function). The results from several studies suggest a coordinated response of several (or all) of these factors might be involved, but this has never been comprehensively evaluated in people. We found that fish oil-derived n-3 PUFA supplementation in healthy older adults increased the expression of genes involved in muscle mitochondrial function [74], and others found, although not consistently, it reduces oxidant emission [71] and ADP sensitivity [75] in mitochondria isolated from human muscle. Rats fed fish oil-derived n-3 PUFAs were found to use less oxygen for tension development and were able to work harder, and fatigued later than those fed the control diet [76]. In healthy people participating in an exercise training program, fish oil supplementation shortened the electromechanical delay and increased the rate of force development during maximal voluntary isometric contractions [63], and adding fish oil to the diet of mice and rats improved their motor and sensory nerve conduction speed and protected them from developing diabetic peripheral neuropathy [77, 78]. Studies conducted in rats and healthy middle-aged people found that fish-oil derived n-3 PUFAs augment brachial artery dilation, vascular conductance, and blood flow [79, 80]. It is therefore likely that several mechanisms contribute to the beneficial effect of fish oil-derived n-3 PUFA on muscle function and further work is needed to investigate this in people.

Summary

An effective approach to prevent and treat age-associated sarcopenia is much needed. Regular physical activity and exercise training have potent anti-sarcopenic effects but are difficult to implement. The current recommendation for increased protein intake is not evidence-based, and could have adverse “side-effects” on cardiometabolic health. Dietary supplementation with ≥2 g of fish oil-derived n-3 PUFAs per day has been found to increase muscle protein synthesis and muscle mass and function in healthy untrained and exercise training older adults but the mechanisms mediating the beneficial effects of fish oil-derived n-3 PUFAs on muscle mass and function have not been fully elucidated.

Conclusion

The results from studies conducted in healthy and exercise training older adults support the use of fish oil-derived n-3 PUFA as a new treatment modality for the prevention and treatment of sarcopenia. Interdisciplinary basic and clinical and translational studies are needed to explore the multifactorial mechanisms responsible for the beneficial effects of fish oil-derived n-3 PUFAs on muscle mass and function.

Key points

- Ageing is associated with a progressive decrease in muscle mass and function, which can have deleterious consequences affecting people's mobility and independence.
- There are currently no effective pharmacological treatments for the treatment and prevention of sarcopenia; lifestyle changes, such as resistance exercise training and high protein intake, are therefore promoted albeit with limited success because of low adherence to exercise and uncertainties concerning the effectiveness of high protein intake elicit the desired increase in muscle mass and function.
- The results from recent studies suggest that dietary supplementation with fish oil-derived n-3 PUFA improves muscle mass and function in both sedentary and exercise training older adults.
- The exact mechanisms by which fish oil-derived n-3 PUFAs exert their beneficial effects on muscle mass and function remain to be elucidated.

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Conflicts of interest

None

Figure legend

Figure 1. Potential mechanisms responsible for the beneficial effects of fish oil-derived n-3 polyunsaturated fatty acids on muscle mass and function. See text for details.

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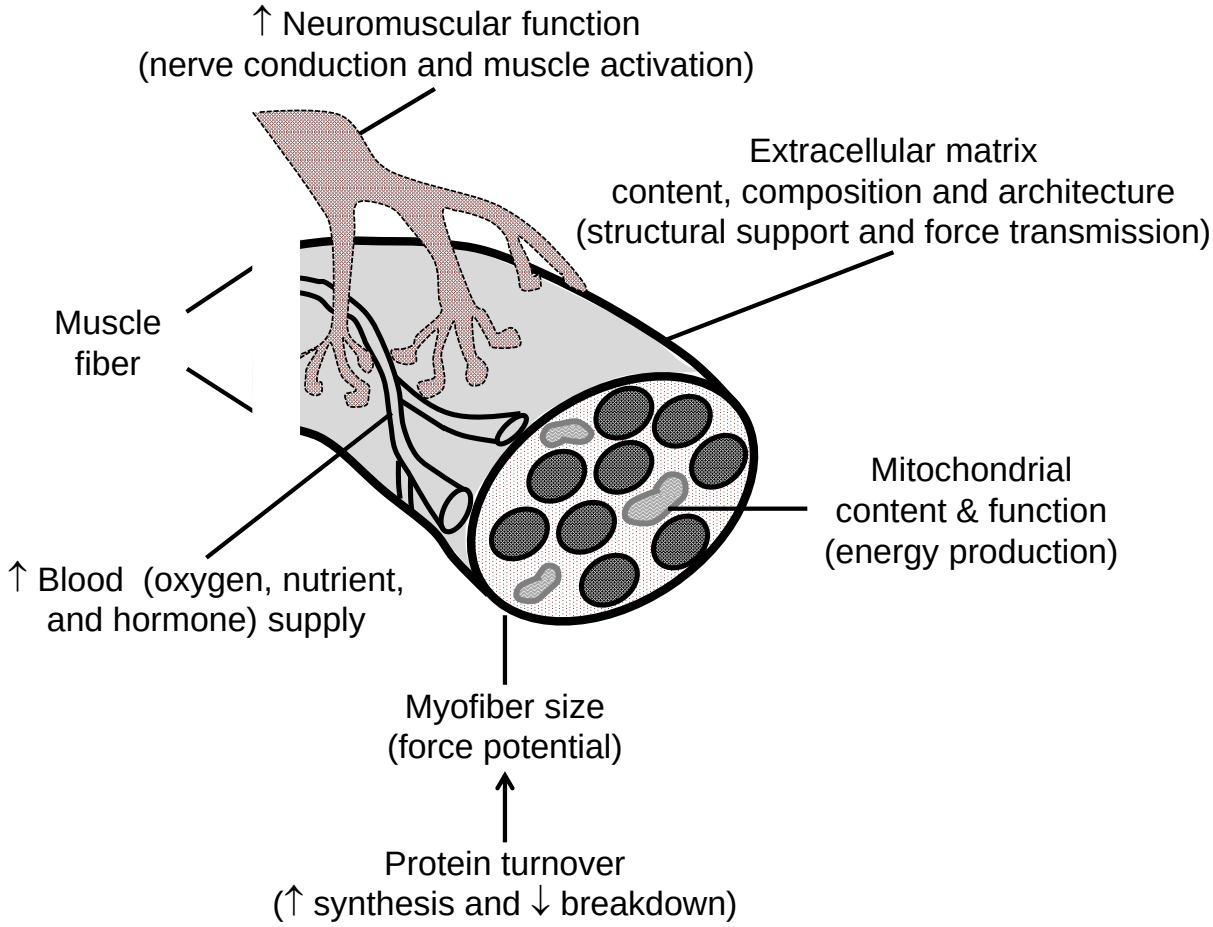

Figure 1. Potential mechanisms responsible for the beneficial effects of fish oil-derived n-3 polyunsaturated fatty acids on muscle mass and function. See text for details.

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