

The Role of n-3 PUFA on Muscle Mass and Function in Aging Humans

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Abstract

Starting in middle age, muscle mass and function decline progressively, which can affect people's mobility and independence late in life. The results from several recent studies demonstrate that dietary supplementation with fish oil-derived from n-3 polyunsaturated fatty acids (PUFA) stimulates muscle protein synthesis, improves muscle mass and function in sedentary older adults, and augments the resistance exercise training-induced increase in muscle strength in 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.

Introduction

Starting in late middle age, skeletal muscles atrophy progressively and muscle tissue undergoes morphological changes (e.g., infiltration with noncontractile 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 to 1% and 1 to 2% per decade, respectively; periods of acute illness and chronic diseases accelerate these processes^{1,3} in part as a result of the underlying disease processes that can affect muscle, but also because of the associated reduction in physical activity, which can have detrimental consequences in older adults because the resulting loss of muscle mass (~5 to 8% after only one to two weeks of reduced ambulation) and function (~10% decrease in strength after only four days of immobilization) are difficult to recover even with intense physical rehabilitation.⁴⁻¹⁰ Although increasing protein intake is often recommended to preserve muscle mass during aging,^{11,12} conclusive evidence that high-protein intake has meaningful effects on muscle mass and/or function is missing.¹³⁻¹⁹ This is most likely due to the saturable relationship between protein intake and muscle protein synthesis after a meal, which reaches a maximum at ~20 to 30 grams,^{23,24} combined with anabolic resistance of aging muscle (i.e.,

Glossary of Abbreviations

ADP: Adenosine Diphosphate

PUFA: Polyunsaturated Fatty Acids

the inability to adequately stimulate protein synthesis and suppress protein breakdown in response to postprandial hyperaminoacidemia-hyperinsulinemia).²⁰⁻²² Recently, fish oil-derived

n-3 PUFAs, i.e., eicosapentaenoic and docosahexaenoic acid, have emerged as a potential new treatment modality for the prevention and treatment of age-associated loss of muscle mass.

Effect of Fish Oil-Derived n-3 PUFA on Muscle Mass and Function

The results from epidemiological studies²⁵ and experiments in cell cultures and animals²⁶ suggest that fish oil-derived n-3 PUFA could have therapeutic effects in older adults. We²⁷ and another group of investigators²⁸ found that healthy, older women who participated in an exercise-training program and consumed 2 to 4 grams of fish oil per day for three months had greater training-induced gains in muscle strength than those who did not supplement their diet with fish oil. We also found six months of dietary supplementation with 4 grams of fish oil-derived n-3 PUFA increased muscle mass and strength in healthy, physically active but untrained older adults.²⁹ Daily supplementation with 1.3 grams 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.³⁰ 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 grams of fish oil-derived n-3 PUFA per day.²⁹

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. We found that adding 4 grams of fish oil-derived n-3 PUFA per day for eight weeks to the diet of healthy older adults increased the acute amino acid-induced activation of the mTOR-p70s6k signaling pathway and muscle protein synthesis.²⁰ Others found that adding 3.9 grams of fish oil-derived n-3 PUFA to the diet of older adults augmented the acute exercise-induced increase in muscle protein synthesis.³¹ The effect of fish

oil-derived n-3 PUFAs on muscle protein synthesis also has been investigated in young adults, and the results are equivocal. We found that eight weeks of fish oil-derived n-3 PUFA intake (4 grams per day) increased the rate of muscle protein synthesis during amino acid and insulin infusion in sedentary young adults.³² On the other hand, others found no effect of eight weeks of fish oil-derived n-3 PUFA intake (5 grams per day) on the rate of muscle protein synthesis in resistance-trained young men, who consumed 30 grams of protein at rest or after a bout of resistance exercise.³³ This was likely because the high protein intake combined with regular exercise training already maximally stimulated muscle protein synthesis in this participant group.²⁴ Studies conducted in cell cultures, rats and patients on maintenance hemodialysis found fish oil-derived n-3 PUFA also attenuated muscle protein breakdown.²⁶

Increased muscle function (strength and endurance) could be due to changes in myocytes themselves (myofiber microstructure, contractility and energy production), as well as to 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 may 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,³⁴ and others found, though not consistently, it reduces oxidant emission³¹ and adenosine diphosphate (ADP) sensitivity³⁵ in mitochondria isolated from human muscle. Rats fed fish oil-derived n-3 PUFAs were found to use less oxygen for tension development, were able to work harder and fatigued later than those fed the control diet.³⁶ 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,²⁸ 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.^{37,38} Studies conducted in rats and healthy middle-aged people found that fish-oil derived n-3 PUFAs also augment brachial artery dilation, vascular conductance and blood flow.^{39,40}

Summary

Fish-oil derived n-3 PUFAs are a potential new treatment modality to prevent and reverse the age-associated loss of muscle mass and function.

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