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

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26

27 **Abstract**

28

29 **Purpose of review:** Muscle mass and function decline progressively starting in middle age,  
30 which can result in sarcopenia and affect people's mobility and independence late in life.

31 Exercise training and increased protein intake are typically recommended to counteract the age-  
32 associated decline in muscle mass and function. However, few people comply with exercise  
33 recommendations and evidence for the anti-sarcopenic effectiveness of high protein intake is  
34 lacking. This review aims to explore recent developments in the potential for fish-oil derived n-3  
35 polyunsaturated fatty acids (n-3 PUFA) to improve muscle mass and function in older people.

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

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

43

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

45

## 46 **Introduction**

47 Starting in late middle-age, skeletal muscles atrophy progressively and muscle tissue  
48 undergoes morphological changes (e.g., infiltration with non-contractile material, such as fat and  
49 connective tissue; reduced capillary density and mitochondrial content; motor unit and  
50 neuromuscular junction remodelling) which can reduce muscles' ability to generate and maintain  
51 force, and negatively affect activities of daily living (walking, climbing stairs, lifting items) [1-3].  
52 In healthy people muscle mass and strength decline by ~0.5%-1.0% and 1%-2% per decade,  
53 respectively; periods of acute illness and chronic diseases accelerate these processes. A  
54 decrease in muscle mass and physical abilities (walking speed and/or strength) below certain  
55 threshold values, established by the *International Sarcopenia Initiative* [1], is referred to as  
56 sarcopenia. Sarcopenia is associated with a 2-3-fold increased risk of falls (~20% increase in  
57 incidence for each ~15% decrease in leg strength), frailty, disability, loss of independence, and  
58 mortality (~4% increase for every 1 kg decrease in grip strength) [1, 4-9]. Sarcopenia affects  
59 10-30% of independently living older adults, without major illness, and even more ill and/or  
60 institutionalized older adults [1, 10-12]. The total number of people affected by sarcopenia is  
61 expected to rise significantly because, according to U.S. Census Bureau Population Projections  
62 ([www.agingstats.gov](http://www.agingstats.gov)), the number of older adults (>65 years of age) is expected to double in 25  
63 years, until the youngest Baby Boomers" reach 65 years of age. No safe and effective drug  
64 therapies for the prevention and treatment of sarcopenia exist. Current recommendations,  
65 therefore, focus on exercise training and high protein intake, but these approaches have  
66 limitations as outlined below. Fish oil-derived n-3 polyunsaturated fatty acids (n-3 PUFA)  
67 (eicosapentaenoic and docosahexaenoic acid) have emerged as a potential new treatment  
68 modality for the prevention and treatment of sarcopenia that warrant serious consideration in the  
69 clinical care for older adults.

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71

## 72 **Physical activity and the risk of sarcopenia**

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

86

## 87 **Current dietary recommendations to mitigate the risk and consequences of sarcopenia**

88 International expert groups recommend a minimum protein intake of 1.0-1.2 g per kg body  
89 weight per day (which is 25%-50% more than the RDA of 0.8 g/kg/d) for healthy older adults,  
90 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  
91 of acute illness [14, 15]. However, conclusive evidence that high protein intake has meaningful  
92 effects on muscle mass and/or function is lacking [27-33]. This may in part be due to the short  
93 duration of many of the studies which have evaluated the effect of protein intake on muscle  
94 mass and strength, but also because most studies paid little attention to participants' habitual  
95 protein intake, the source of protein and the timing of protein intake. High intake of leucine-rich  
96 proteins, such as whey protein, evenly distributed across meals is suggested to be particularly  
97 beneficial because protein ingestion stimulates muscle protein synthesis acutely in a dose

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

115

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

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

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

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

149 [38]. Studies conducted in cell cultures, rats, and patients on maintenance hemodialysis found  
150 fish oil-derived n-3 PUFA also attenuated muscle protein breakdown [61]. The effect of fish oil-  
151 derived n-3 PUFAs on muscle cell turnover is not known.

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

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173

174 **Summary**

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

183

184 **Conclusion**

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

190

191 **Key points**

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

204

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213

214 **Conflicts of interest**

215 None

216

217 **Figure legend**

218

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

221

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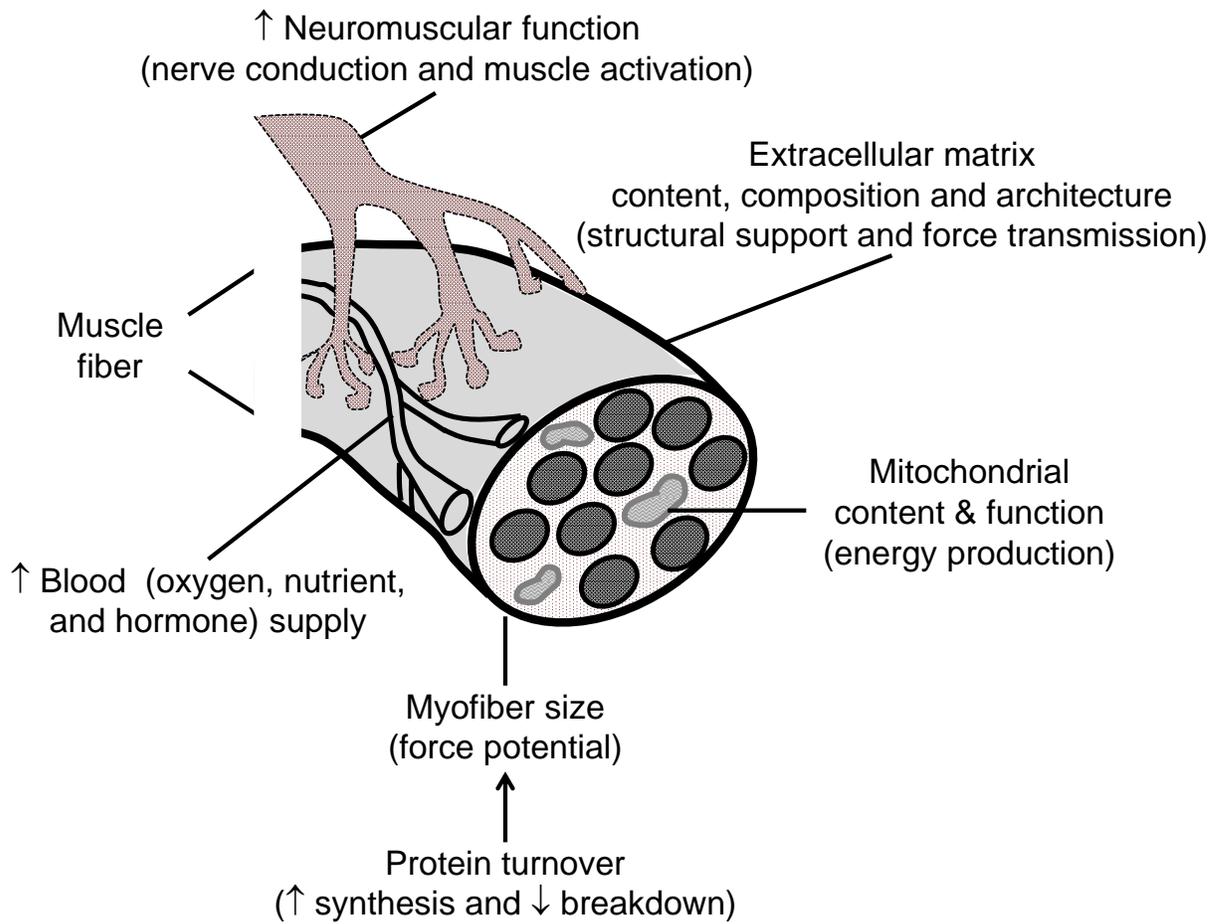
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**Figure 1.** Potential mechanisms responsible for the beneficial effects of fish oil-derived n-3 polyunsaturated fatty acids on muscle mass and function. See text for details.