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The Effects of Dietary Omega-3s on Muscle Composition and Quality in Older Adults

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Abstract

This review will focus on findings from the few studies performed to date in humans to examine changes in muscle protein turnover, lean or muscle mass and physical function following fish oil-derived omega-3 fatty acid treatment. Although considerable gaps in our current knowledge exist, hypertrophic responses (e.g., improvements in the rate of muscle protein synthesis and mTOR signaling during increased amino acid availability and an increase in muscle volume) have been reported in older adults following prolonged (8 to 24 weeks) of omega-3 fatty acid supplementation. There is also accumulating evidence that increased omega-3 fatty acid levels in red blood cells are positively related to strength and measures of physical function. As a result, increased omega-3 fatty acid consumption may prove to be a promising low-cost dietary approach to attenuate or prevent aging associated declines in muscle mass and function.

Keywords

Fish oil; mTOR; muscle protein synthesis; muscle protein breakdown; eicosapentaenoic acid; docosahexaenoic acid

Introduction

Aging is associated with a progressive loss of muscle mass and function, a condition frequently termed ‘sarcopenia’ [1, 2]. The extent of the aging-induced decline in muscle mass and strength has been linked to a greater risk of physical impairment, reduced quality of life and death [1, 2] with healthcare costs associated with sarcopenia estimated to cost $18.5 billion per year in the United States in 2000 [3]. As a result, development of low-cost therapeutic approaches to combat the deleterious effects of sarcopenia are vitally important to a U.S. population projected to become considerably older over the coming decades [4]. One simple and promising approach may be to increase dietary omega-3 fatty acid consumption and this review will discuss whether current evidence supports omega-3 fatty

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Conflict of Interest

Gordon I. Smith declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

acid induced improvements in muscle protein turnover, mass and strength in older adults. Areas in need of further study to advance or clarify our understanding of the metabolic effects of omega-3 fatty acids will be highlighted. Finally, while the primary focus of this review will be on responses in older adults, where data only exists in other populations or in animal and cell models these results will be discussed in the context of aging.

Regulation of muscle mass

Muscle mass is determined by the balance of the rates of muscle protein synthesis (MPS) and breakdown (MPB) with skeletal muscle protein turnover a tightly controlled process in healthy adults, typically proceeding at a rate of ~1–2% per day. Muscle hypertrophy occurs when MPS > MPB with muscle atrophy prevalent when MPB > MPS. Although rates of MPS and MPB fluctuate throughout the day the majority of time is spent in the postabsorptive state where the rate of MPB is ~30–40% greater than MPS [5, 6]. Periods of muscle protein accretion (i.e., MPS > MPB) therefore only occur intermittently and are typically limited to following protein/mixed meal ingestion where increased circulating amino acid and insulin concentrations stimulate MPS and inhibit MPB. While MPB is sensitive to small increases in insulin concentration, with maximal suppression in MPB occurring at relatively low levels (i.e., ~30 μU/mL) [7], amino acids stimulate MPS in a dose response manner with maximal responses observed following consumption of ~20 g protein in young, healthy individuals [8–10]. Consumption of greater amounts of protein are not effective in further stimulating MPS and instead result in oxidation of the excess amino acids [10]. The stimulatory effect of acute hyperaminoacidemia on MPS is short-lived, lasting ~90 min [11, 12] after which MPS returns to baseline even in the presence of sustained elevations in plasma amino acid concentration [11, 12]; a phenomenon recently termed the “muscle-full effect” [12]. A refractory period of an unknown duration is then required before MPS can again be stimulated by further protein/amino acid administration. Resistance exercise in the postabsorptive state also stimulates MPS but protein balance remains negative as MPB is also increased, although to a lesser extent than MPS [13, 14]. Net positive protein balance following exercise therefore only occurs when protein is consumed during the post-exercise period, which results in greater MPS and protein balance compared to protein ingestion or exercise alone [15, 16, 14]. In young, healthy individuals periods of positive net protein balance are counterbalanced by periods of negative net balance such that muscle mass is typically maintained during early adulthood [17].

In older adults a decrease in fasting MPS has been observed by some groups [18–21]. Aging-induced declines in MPS are, however, likely confined to frail individuals with rates of fasting MPS and MPB reported to be similar in healthy young and older adults [19, 5, 22, 8, 23]. As a result, the current paradigm is for muscle atrophy to occur in the majority of older adults due to blunted responses to previously anabolic stimuli such as protein ingestion/amino acid administration and resistance exercise [24, 25]. There is considerably less information on the effect of aging on MPB compared with MPS, however, it appears that the ability of insulin to suppress MPB is also blunted with aging [26]. As a consequence of aging-induced dysregulation of MPS (and probably also MPB) muscle mass loss occurs at a rate of ~0.5–1.0% per year from the 5^{th} or 6^{th} decade onwards [17] with a greater rate of muscle loss observed during times of illness and reduced mobility [27].

Determinants of muscle strength and function with aging

The maximum force produced by individual muscle fibers is largely determined by the fiber type (i.e., type II > type I) and the cross-sectional area [28]. As a result, negligible differences in peak power have been reported between muscle fibers from young or older adults in the *ex vivo* setting when results are normalized to fiber size [28]. This finding differs to in intact humans where the deterioration in muscle function occurs at ~2–3-fold greater rate than the loss of muscle mass (declines of ~2–3% vs. ~0.5–1.0% per year, respectively) [29, 30]. The reduction in muscle quality (i.e., strength per unit of muscle mass) with aging has been postulated to be occur due to changes in the muscle architecture [31], an increase in intermuscular fat infiltration [32–34], greater muscle fibrosis [35, 36], and reduced neuromuscular activation [37, 38].

Omega-3 fatty acid intake

Omega-3 fatty acids are polyunsaturated fatty acids that contain a double bond at the third carbon from the methyl end of the chain. Humans, as with all other mammals, are unable to synthesis omega-3 fatty acids *de novo* and as a result they are essential to the diet. In the United States total omega-3 fatty acid intake is typically between 1.4 and 1.6 g per day [39–41] with the majority (~90%) consumed as α-linolenic acid (ALA; C18:3*n-3*); a fatty acid found in many plants, nuts, seeds and vegetable oils. The ability for humans to elongate and desaturate ALA to produce eicosapentaenoic acid (EPA; C20:5*n-3*) and docosahexaenoic acid (DHA; C22:6*n-3*), thought to be the most bioactive omega-3 fatty acids, is extremely limited with <4% of ALA converted to DHA in men [42–45] and <10% converted to DHA in women [46]. Intake of EPA and DHA, which are found in oily fish such as salmon, mackerel and sardines, is low in the United States with only ~0.1–0.2 g EPA and DHA typically consumed per day [39–41]; a level that is substantially lower than the currently recommended intake of ≈0.5 g per day in healthy individuals [47] and ≈1 g per day for individuals with documented cardiovascular disease [48].

Increased consumption of fatty fish in the diet or intake of omega-3 fatty acid supplements can markedly increase tissue and cellular omega-3 fatty acid content in a dose response manner [49, 50]. Incorporation of omega-3 fatty acids into lipid membranes occurs very slowly; taking ~6 months to reach its zenith in red blood cells in healthy men [49]. In addition, there is considerable variability in the omega-3 fatty acid content of different tissues and cells with a ~50% higher omega-3 fatty acid content found in erythrocytes than in muscle phospholipids [51]. Nonetheless, a doubling in EPA and DHA content in muscle phospholipids can still be observed when omega-3 fatty acids are supplemented at relatively large doses (i.e., 4 g/d) for 8 wk [52, 53].

Positive associations between age and EPA and DHA content in red blood cells and plasma phospholipid have been frequently reported [54–57]; a finding likely attributable to greater EPA and DHA intake in the older subjects rather than an increased ability to elongate and desaturate ALA in older age [54, 56, 57]. Moreover, the difference in red blood cell and plasma phospholipid EPA and DHA content between young and older adults, is considerably smaller than increase in EPA and DHA content typically observed after omega-3 fatty acid

supplementation [52, 50, 49, 53] (~20–25% difference vs. 200–300% increase, respectively) [54–56, 52, 50, 49, 53].

Muscle protein metabolism

There is considerable evidence from animal and *in vitro* models supporting a stimulatory effect of omega-3 fatty acids on MPS. For example, a greater anabolic response to mixed nutrient feeding was observed following consumption of a DHA-enriched diet for 34 days in growing pigs with no effect on fasting MPS [58]. This response is similar to observed in C2C12 myotubes with EPA treatment having no effect on MPS in the amino acid starved state but inducing a greater MPS response to increased leucine availability [59]. In both studies omega-3 fatty acid-induced stimulation of MPS occurred concomitant to greater signaling through the mTOR pathway [59, 58]; a feature of omega-3 fatty acid supplementation also reported in growing steer in the fed state [60].

To determine whether similar responses are observed in humans we randomized non-obese older adults (aged 65 to 81 y) to supplement with either 4 g/d Lovaza® (GlaxoSmithKline, Research Triangle Park, North Carolina, USA) containing 1.86 g EPA and 1.50 g DHA or an equivalent dose of corn oil (control group) for 8 wk [52]. Rates of MPS in the postabsorptive state and in response to insulin and amino acid infusion were determined before and after supplementation. In subjects randomized to supplement with corn oil no change in muscle phospholipid composition, fasting MPS or MPS during amino acid and insulin infusion was observed. In contrast, omega-3 fatty acid supplementation doubled the EPA and DHA content in muscle phospholipids and resulted in a ~3-fold greater hyperaminoacidemia-hyperinsulinemia–induced increase in MPS (from 0.009 ± 0.005 %·h^{-1} above basal values to 0.031 ± 0.003 %·h^{-1} above basal values; $P < 0.01$), which occurred in parallel to ~50% greater activation (assessed by degree of phosphorylation) of the p70s6k-mTOR pathway [52]. In a follow-up study we observed similar responses (i.e., greater MPS and mTOR activation during insulin and amino acid infusion) in younger individuals aged between 25 and 45 years [53]. Specifically, MPS during hyperaminoacidemia-hyperinsulinemia increased from 0.027 ± 0.005 %·h^{-1} to 0.042 ± 0.005 %·h^{-1} ($P = 0.01$) above basal, postabsorptive rates following omega-3 fatty acid supplementation in our younger participants, which coincided with a ~50% greater increase in muscle p70s6k and mTOR phosphorylation. Our observations in both young and older adults are therefore remarkably consistent with those reported in animal models and in cell culture [60, 58, 59] and together suggest that omega-3 fatty acids enhance the MPS response to nutritional stimuli without affecting MPS in the postabsorptive state. Despite convincing evidence that omega-3 fatty acids act through the mTOR pathway [52, 59, 60, 58, 53], the mechanism(s) for the increased activation of this pathway are presently unknown. Current dogma is that omega-3 fatty acids principally act by reducing the inflammatory state, however, in both our young and older subjects no change in plasma inflammatory markers (C-reactive protein, tumor necrosis factor-α, and interleukin-6) was observed [52, 53]; presumably due to their low circulating levels prior to supplementation. Nonetheless, we cannot rule out that reductions in local inflammatory signaling (i.e., within skeletal muscle itself) occur, and this possibility requires further study. Alternatively, omega-3 fatty acid supplementation may increase MPS by further stimulating blood flow during hyperaminoacidemia-hyperinsulinemia with

improvements in endothelial function frequently reported following omega-3 fatty acid treatment [61–64]. The ability of insulin to increase blood flow during times of feeding is blunted with aging [65], which reduces the rate of amino acid delivery to the muscle [66, 67] and is a major contributory factor to the etiology of aging-induced anabolic resistance [66, 68].

Work to date has almost entirely focused on the effect of omega-3 fatty acids on changes in MPS with limited information on its effect on MPB and no information on MPB in humans. *In vitro* studies in C2C12 myotubes [59] and *ex vivo* studies in rodents [69–71] do, however, overwhelmingly suggest omega-3 fatty acids inhibit MPB, which when coupled with an augmented MPS should further improve net protein balance and muscle accretion.

Muscle and lean body mass

Based on muscle protein turnover responses to omega-3 fatty acid supplementation one would expect a paralleled increase in muscle mass. There is, however, little consensus on the effect of omega-3 fatty acid supplementation on lean body or fat-free mass in the weight stable state in relatively healthy adults. For example, 4 studies to date have reported lean body or fat-free mass to be unchanged following omega-3 fatty acid supplementation [72–74, 62] with 2 additional studies reporting 1–4% increases in lean body mass [75, 76]. Although the discrepant findings may simply be due to the short duration of all of these studies (i.e., 3 to 12 weeks) there is circumstantial evidence that a minimum dose of omega-3 fatty acids (>2 g EPA and DHA per day) may be required before an anabolic response is observed. In support of this notion, when 0.51 to 1.8 g EPA and DHA per day was provided non-significant results were presented [72–74, 62] with increases in lean body mass confined to those studies giving 2.4 to 3.0 g EPA and DHA per day [75, 76]. One important limitation of these studies, and by extension the minimum effective dose hypothesis, is that without exception whole-body lean mass was examined (by dual-energy X-ray absorptiometry, air displacement plethysmography or bioelectrical impedance analysis) with muscle only contributing ~50% to total body lean mass [77]. As a result, small but still physiologically significant changes in muscle mass may go undetected using these whole-body approaches. To overcome this limitation, we recently performed a randomized, controlled double-blind study to examine whether omega-3 fatty acid supplementation affects thigh muscle volume measured by magnetic resonance imaging (MRI) [78]. Sixty healthy, older adults (aged 60 – 81 yr) consumed either 4 g per day of Lovaza® (GlaxoSmithKline, Research Triangle Park, North Carolina, USA), which contains 1.86 g EPA and 1.50 g DHA, or 4 g of corn oil (control) per day for 6 months with no change in muscle volume found in the control group. In contrast, a 2.2% (95% CI: 0.3 to 4.2%) increase in muscle volume above baseline was found in the omega-3 fatty acid group with a treatment effect (i.e., compared to responses in the control group) of 3.6% (95% CI: 0.2 to 7.0%). While the omega-3 fatty acid-induced change in muscle volume in this study was smaller than reported following resistance exercise in older adults [79–81], the magnitude of the increase was still highly clinically relevant; being equivalent to the amount of muscle lost over a ~3 yr period [1, 2, 30]. Despite these encouraging findings, many questions still remain unanswered. For example the most effective dose and treatment duration are currently unknown. In addition, it will be important to translate our findings in

healthy older adults into more vulnerable populations such as frail and sarcopenic individuals and to study responses in older adults experiencing periods of rapid muscle loss such as during limb immobilization and bed rest.

Strength and Physical function

Results from cross-sectional studies in older adults have consistently reported positive associations between omega-3 fatty acid intake, greater hand-grip, 1-repetition maximum leg press and isokinetic knee extension strength and faster chair rise times [82–84]. To confirm the results from these earlier observational studies we recently conducted a randomized controlled, double blind study to examine the effect of omega-3 fatty acid or corn oil (control) supplementation for 6 months on grip strength, 1-repetition maximum strength for several upper and lower exercises and isometric power in healthy, older adults [78]. No change in any outcome was observed after 3 months of supplementation, however, treatment effects for hand grip of 2.3 kg (~6.5%) and 1-RM muscle strength of 9.1 kg (4.0%) were apparent at the end of the study with a trend for isometric power to also be improved. Reassuringly, the magnitude of the improvements we observed were consistent with those reported from previous cross-sectional studies [82] and were clinically relevant, equating to prevention of the aging-associated losses of function that occurs over a ~2–3 yr period [30, 29]. These data suggest that omega-3 fatty acid administration improves muscle strength and function in older adults but there may be a significant latency period before detectable improvements in physical function manifest; a process that could take between ~3 to 6 months. Greater improvements in lower limb isometric peak torque and chair raising performance following exercise training in older adults have also been observed in subjects supplementing with omega-3 fatty acids compared with exercise training alone [85]. Whether the omega-3 fatty acid-induced improvements in muscle strength and function observed by our group and others [76, 78, 85] are solely related to gains in muscle mass or are instead influenced by improvements in muscle quality is unclear. However, results from our recent study, where increases in strength following omega-3 fatty acid supplementation were ~2-fold greater than the gain in muscle volume [78], provide at least some circumstantial evidence for an omega-3 fatty acid-induced improvement in muscle quality. Additionally, omega-3 fatty acid supplementation has been reported to improve neuromuscular function [85, 86] and reduce intermuscular fat infiltration [78], both of which help determine muscle quality and have been implicated in aging-induced declines in muscle function [37, 38, 32–34]. Changes in other factors that influence muscle quality such as muscle architecture [31], and fibrosis [35, 36] have to the author's knowledge not been examined in response to omega-3 fatty acids.

Conclusions

There is growing evidence that fish-oil derived omega-3 fatty acids stimulate gains in muscle mass in older adults by overcoming aging-induced anabolic resistance. More importantly, omega-3 fatty acid supplementation may also improve strength and muscle function due to a combination of the increased muscle mass and potentially an improvement in muscle quality. Many questions still remain unanswered however, including whether omega-3 fatty acid-induced improvements in MPS, muscle volume and muscle function occur in a dose

dependent manner, the latency (if any) and duration of the beneficial responses, whether all populations respond similarly or there is something unique to the healthy individuals that have been studied to date and finally to elucidate the individual roles EPA and DHA play in regulating muscle anabolism and strength in humans. As a result, while omega-3 fatty acids appear to be a promising therapeutic approach to prevent aging associated declines in muscle mass and function there is considerable scope for future work to fully elucidate its anabolic potential.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011; 12(4):249–56. [PubMed: 21527165]
2. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010; 39(4):412–23. [PubMed: 20392703]
3. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. J Am Geriatr Soc. 2004; 52(1):80–5. [PubMed: 14687319]
4. Vincent, GK.; Velkoff, VA. Current population reports. U.S. Census Bureau; Washington, D.C.: 2010. The Next Four Decades: The Older Population in the United States: 2010 to 2050. P25-1138
5. Volpi E, Sheffield-Moore M, Rasmussen BB, Wolfe RR. Basal muscle amino acid kinetics and protein synthesis in healthy young and older men. Jama. 2001; 286(10):1206–12. [PubMed: 11559266]
6. Fujita S, Rasmussen BB, Bell JA, Cadenas JG, Volpi E. Basal muscle intracellular amino acid kinetics in women and men. Am J Physiol Endocrinol Metab. 2007; 292(1):E77–83. [PubMed: 16896165]
7. Greenhaff PL, Karagounis LG, Peirce N, Simpson EJ, Hazell M, Layfield R, et al. Disassociation between the effects of amino acids and insulin on signaling, ubiquitin ligases, and protein turnover in human muscle. Am J Physiol Endocrinol Metab. 2008; 295(3):E595–604. [PubMed: 18577697]
8. Cuthbertson D, Smith K, Babraj J, Leese G, Waddell T, Atherton P, et al. Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. FASEB J. 2005; 19(3):422–4. [PubMed: 15596483]
9. Bohe J, Low A, Wolfe RR, Rennie MJ. Human muscle protein synthesis is modulated by extracellular, not intramuscular amino acid availability: a dose-response study. J Physiol. 2003; 552(1):315–24. [PubMed: 12909668]
10. Moore DR, Robinson MJ, Fry JL, Tang JE, Glover EI, Wilkinson SB, et al. Ingested protein dose response of muscle and albumin protein synthesis after resistance exercise in young men. Am J Clin Nutr. 2009; 89(1):161–8. [PubMed: 19056590]

11. Bohe J, Low JF, Wolfe RR, Rennie MJ. Latency and duration of stimulation of human muscle protein synthesis during continuous infusion of amino acids. J Physiol. 2001; 532(Pt 2):575–9. [PubMed: 11306673]
12. Atherton PJ, Etheridge T, Watt PW, Wilkinson D, Selby A, Rankin D, et al. Muscle full effect after oral protein: time-dependent concordance and discordance between human muscle protein synthesis and mTORC1 signaling. Am J Clin Nutr. 2010; 92:1080–8. [PubMed: 20844073]
13. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. Am J Physiol. 1997; 273(1):E99–107. [PubMed: 9252485]
14. Tipton KD, Ferrando AA, Phillips SM, Doyle D Jr, Wolfe RR. Postexercise net protein synthesis in human muscle from orally administered amino acids. Am J Physiol. 1999; 276(4 Pt 1):E628–34. [PubMed: 10198297]
15. Biolo G, Tipton KD, Klein S, Wolfe RR. An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. Am J Physiol. 1997; 273:E122–E9. [PubMed: 9252488]
16. Rasmussen BB, Tipton KD, Miller SL, Wolf SE, Wolfe RR. An oral essential amino acid-carbohydrate supplement enhances muscle protein anabolism after resistance exercise. J Appl Physiol. 2000; 88(2):386–92. [PubMed: 10658002]
17. Kyle UG, Genton L, Hans D, Karsegard L, Slosman DO, Pichard C. Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. Eur J Clin Nutr. 2001; 55(8):663–72. [PubMed: 11477465]
18. Chevalier S, Gougeon R, Nayar K, Morais JA. Frailty amplifies the effects of aging on protein metabolism: role of protein intake. Am J Clin Nutr. 2003; 78(3):422–9. [PubMed: 12936924]
19. Dorrens J, Rennie MJ. Effects of ageing and human whole body and muscle protein turnover. Scand J Med Sci Sports. 2003; 13(1):26–33. [PubMed: 12535314]
20. Balagopal P, Rooyackers OE, Adey DB, Ades PA, Nair KS. Effects of aging on in vivo synthesis of skeletal muscle myosin heavy-chain and sarcoplasmic protein in humans. Am J Physiol. 1997; 273(4 Pt 1):E790–800. [PubMed: 9357810]
21. Welle S, Thornton C, Jozefowicz R, Statt M. Myofibrillar protein synthesis in young and old men. Am J Physiol. 1993; 264(5 Pt 1):E693–8. [PubMed: 8498491]
22. Guillet C, Prod'homme M, Balage M, Gachon P, Giraudet C, Morin L, et al. Impaired anabolic response of muscle protein synthesis is associated with S6K1 dysregulation in elderly humans. Faseb J. 2004; 18(13):1586–7. [PubMed: 15319361]
23. Koopman R, van Loon LJ. Aging, exercise, and muscle protein metabolism. J Appl Physiol. 2009; 106(6):2040–8. [PubMed: 19131471]
24. Kumar V, Selby A, Rankin D, Patel R, Atherton P, Hildebrandt W, et al. Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. J Physiol. 2009; 587(1):211–7. [PubMed: 19001042]
25. Moore DR, Churchward-Venne TA, Witard O, Breen L, Burd NA, Tipton KD, et al. Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. J Gerontol A Biol Sci Med Sci. 2015; 70(1):57–62. [PubMed: 25056502]
26. Wilkes EA, Selby AL, Atherton PJ, Patel R, Rankin D, Smith K, et al. Blunting of insulin inhibition of proteolysis in legs of older subjects may contribute to age-related sarcopenia. Am J Clin Nutr. 2009; 90(5):1343–50. [PubMed: 19740975]
27. Buford TW, Anton SD, Judge AR, Marzetti E, Wohlgemuth SE, Carter CS, et al. Models of accelerated sarcopenia: critical pieces for solving the puzzle of age-related muscle atrophy. Ageing Res Rev. 2010; 9(4):369–83. [PubMed: 20438881]
28. Trappe S, Gallagher P, Harber M, Carrithers J, Fluckey J, Trappe T. Single muscle fibre contractile properties in young and old men and women. J Physiol. 2003; 552(Pt 1):47–58. [PubMed: 12837929]
29. Skelton DA, Greig CA, Davies JM, Young A. Strength, power and related functional ability of healthy people aged 65–89 years. Age Ageing. 1994; 23(5):371–7. [PubMed: 7825481]

30. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol A Biol Sci Med Sci. 2006; 61(10):1059–64. [PubMed: 17077199]

31. Stenroth L, Peltonen J, Cronin NJ, Sipila S, Finni T. Age-related differences in Achilles tendon properties and triceps surae muscle architecture in vivo. J Appl Physiol (1985). 2012; 113(10): 1537–44. [PubMed: 23042907]

32. Lorbergs AL, Noseworthy MD, Adachi JD, Stratford PW, MacIntyre NJ. Fat Infiltration in the Leg is Associated with Bone Geometry and Physical Function in Healthy Older Women. Calcif Tissue Int. 2015; 97(4):353–63. [PubMed: 26071112]

33. Marcus RL, Addison O, Kidde JP, Dibble LE, Lastayo PC. Skeletal muscle fat infiltration: impact of age, inactivity, and exercise. J Nutr Health Aging. 2010; 14(5):362–6. [PubMed: 20424803]

34. Beavers KM, Beavers DP, Houston DK, Harris TB, Hue TF, Koster A, et al. Associations between body composition and gait-speed decline: results from the Health, Aging, and Body Composition study. Am J Clin Nutr. 2013; 97(3):552–60. [PubMed: 23364001]

35. Kusko RL, Banerjee C, Long KK, Darcy A, Otis J, Sebastiani P, et al. Premature expression of a muscle fibrosis axis in chronic HIV infection. Skelet Muscle. 2012; 2(1):10. [PubMed: 22676806]

36. Brack AS, Conboy MJ, Roy S, Lee M, Kuo CJ, Keller C, et al. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science. 2007; 317(5839):807–10. [PubMed: 17690295]

37. Plow EB, Varnerin N, Cunningham DA, Janini D, Bonnett C, Wyant A, et al. Age-related weakness of proximal muscle studied with motor cortical mapping: a TMS study. PLoS ONE. 2014; 9(2):e89371. [PubMed: 24586726]

38. Plow EB, Cunningham DA, Bonnett C, Gohar D, Bayram M, Wyant A, et al. Neurophysiological correlates of aging-related muscle weakness. J Neurophysiol. 2013; 110(11):2563–73. [PubMed: 24027104]

39•. Papanikolaou Y, Brooks J, Reider C, Fulgoni VL 3rd. U.S. adults are not meeting recommended levels for fish and omega-3 fatty acid intake: results of an analysis using observational data from NHANES 2003–2008. Nutr J. 2014; 13:31. This paper uses NHANES data to show that intake of EPA and DHA in the United States is substantially lower than recommended. [PubMed: 24694001]

40. Kris-Etherton PM, Taylor DS, Yu-Poth S, Huth P, Moriarty K, Fishell V, et al. Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr. 2000; 71(1 Suppl):179S–88S. [PubMed: 10617969]

41. Honors MA, Harnack LJ, Zhou X, Steffen LM. Trends in fatty acid intake of adults in the Minneapolis-St Paul, MN Metropolitan Area, 1980–1982 through 2007–2009. J Am Heart Assoc. 2014; 3(5):e001023. [PubMed: 25339343]

42. Burdge GC, Jones AE, Wootton SA. Eicosapentaenoic and docosapentaenoic acids are the principal products of alpha-linolenic acid metabolism in young men*. Br J Nutr. 2002; 88(4):355–63. [PubMed: 12323085]

43. Hussein N, Ah-Sing E, Wilkinson P, Leach C, Griffin BA, Millward DJ. Long-chain conversion of [13C]linoleic acid and alpha-linolenic acid in response to marked changes in their dietary intake in men. J Lipid Res. 2005; 46(2):269–80. [PubMed: 15576848]

44. Emken EA, Adlof RO, Gulley RM. Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males. Biochim Biophys Acta. 1994; 1213(3):277–88. [PubMed: 7914092]

45. Burdge GC, Finnegan YE, Minihane AM, Williams CM, Wootton SA. Effect of altered dietary n-3 fatty acid intake upon plasma lipid fatty acid composition, conversion of [13C]alpha-linolenic acid to longer-chain fatty acids and partitioning towards beta-oxidation in older men. Br J Nutr. 2003; 90(2):311–21. [PubMed: 12908891]

46. Burdge GC, Wootton SA. Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. Br J Nutr. 2002; 88(4):411–20. [PubMed: 12323090]

47. Gebauer SK, Psota TL, Harris WS, Kris-Etherton PM. n-3 fatty acid dietary recommendations and food sources to achieve essentiality and cardiovascular benefits. Am J Clin Nutr. 2006; 83(6 Suppl):1526S–35S. [PubMed: 16841863]

48. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002; 106(21):2747–57. [PubMed: 12438303]

49. Katan MB, Deslypere JP, van Birgelen AP, Penders M, Zegwaard M. Kinetics of the incorporation of dietary fatty acids into serum cholesteryl esters, erythrocyte membranes, and adipose tissue: an 18-month controlled study. J Lipid Res. 1997; 38(10):2012–22. [PubMed: 9374124]

50. Flock MR, Skulas-Ray AC, Harris WS, Etherton TD, Fleming JA, Kris-Etherton PM. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial. J Am Heart Assoc. 2013; 2(6):e000513. [PubMed: 24252845]

51. Di Marino L, Maffettone A, Cipriano P, Sacco M, Di Palma R, Amato B, et al. Is the erythrocyte membrane fatty acid composition a valid index of skeletal muscle membrane fatty acid composition? Metabolism. 2000; 49(9):1164–6. [PubMed: 11016898]

52. Smith GI, Atherton P, Reeds DN, Mohammed BS, Rankin D, Rennie MJ, et al. Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial. Am J Clin Nutr. 2011; 93:402–12. [PubMed: 21159787]

53. Smith GI, Atherton P, Reeds DN, Mohammed BS, Rankin D, Rennie MJ, et al. Omega-3 polyunsaturated fatty acids augment the muscle protein anabolic response to hyperinsulinaemia-hyperaminoacidaemia in healthy young and middle-aged men and women. Clin Sci. 2011; 121(6): 267–78. [PubMed: 21501117]

54. Harris WS, Pottala JV, Varvel SA, Borowski JJ, Ward JN, McConnell JP. Erythrocyte omega-3 fatty acids increase and linoleic acid decreases with age: observations from 160,000 patients. Prostaglandins Leukot Essent Fatty Acids. 2013; 88(4):257–63. [PubMed: 23375840]

55. Itomura M, Fujioka S, Hamazaki K, Kobayashi K, Nagasawa T, Sawazaki S, et al. Factors influencing EPA+DHA levels in red blood cells in Japan. In Vivo. 2008; 22(1):131–5. [PubMed: 18396795]

56. Dewailly EE, Blanchet C, Gingras S, Lemieux S, Sauve L, Bergeron J, et al. Relations between n-3 fatty acid status and cardiovascular disease risk factors among Quebecers. Am J Clin Nutr. 2001; 74(5):603–11. [PubMed: 11684528]

57. Dewailly E, Blanchet C, Lemieux S, Sauve L, Gingras S, Ayotte P, et al. n-3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. Am J Clin Nutr. 2001; 74(4):464–73. [PubMed: 11566644]

58. Wei HK, Zhou Y, Jiang S, Tao YX, Sun H, Peng J. Feeding a DHA-enriched diet increases skeletal muscle protein synthesis in growing pigs: association with increased skeletal muscle insulin action and local mRNA expression of insulin-like growth factor 1. Br J Nutr. 2013; 110(4):671–80. [PubMed: 23433177]

59••. Kamolrat T, Gray SR. The effect of eicosapentaenoic and docosahexaenoic acid on protein synthesis and breakdown in murine C2C12 myotubes. Biochem Biophys Res Commun. 2013; 432(4):593–8. This paper provides evidence that EPA stimulates the rates of protein synthesis and inhibits protein breakdown. [PubMed: 23438435]

60. Gingras AA, White PJ, Chouinard PY, Julien P, Davis TA, Dombrowski L, et al. Long-chain omega-3 fatty acids regulate bovine whole-body protein metabolism by promoting muscle insulin signalling to the Akt-mTOR-S6K1 pathway and insulin sensitivity. J Physiol. 2007; 579(Pt 1):269–84. [PubMed: 17158167]

61. Oh PC, Koh KK, Sakuma I, Lim S, Lee Y, Lee S, et al. Omega-3 fatty acid therapy dose-dependently and significantly decreased triglycerides and improved flow-mediated dilation, however, did not significantly improve insulin sensitivity in patients with hypertriglyceridemia. Int J Cardiol. 2014; 176(3):696–702. [PubMed: 25147070]

62. Hill AM, Buckley JD, Murphy KJ, Howe PR. Combining fish-oil supplements with regular aerobic exercise improves body composition and cardiovascular disease risk factors. Am J Clin Nutr. 2007; 85(5):1267–74. [PubMed: 17490962]

63. Shah AP, Ichiuji AM, Han JK, Traina M, El-Bialy A, Meymandi SK, et al. Cardiovascular and endothelial effects of fish oil supplementation in healthy volunteers. J Cardiovasc Pharmacol Ther. 2007; 12(3):213–9. [PubMed: 17875948]
64. Walser B, Giordano RM, Stebbins CL. Supplementation with omega-3 polyunsaturated fatty acids augments brachial artery dilation and blood flow during forearm contraction. Eur J Appl Physiol. 2006; 97(3):347–54. [PubMed: 16770472]
65. Meneilly GS, Elliot T, Bryer-Ash M, Floras JS. Insulin-mediated increase in blood flow is impaired in the elderly. J Clin Endocrinol Metab. 1995; 80(6):1899–903. [PubMed: 7775638]
66. Rasmussen BB, Fujita S, Wolfe RR, Mittendorfer B, Roy M, Rowe VL, et al. Insulin resistance of muscle protein metabolism in aging. FASEB J. 2006; 20(6):768–9. [PubMed: 16464955]
67. Fujita S, Rasmussen BB, Cadenas JG, Grady JJ, Volpi E. Effect of insulin on human skeletal muscle protein synthesis is modulated by insulin-induced changes in muscle blood flow and amino acid availability. Am J Physiol Endocrinol Metab. 2006; 291(4):E745–54. [PubMed: 16705054]
68. Fujita S, Glynn EL, Timmerman KL, Rasmussen BB, Volpi E. Supraphysiological hyperinsulinaemia is necessary to stimulate skeletal muscle protein anabolism in older adults: evidence of a true age-related insulin resistance of muscle protein metabolism. Diabetologia. 2009; 52(9):1889–98. [PubMed: 19588121]
69. Beck SA, Smith KL, Tisdale MJ. Anticachectic and antitumor effect of eicosapentaenoic acid and its effect on protein turnover. Cancer Res. 1991; 51(22):6089–93. [PubMed: 1657378]
70. Whitehouse AS, Smith HJ, Drake JL, Tisdale MJ. Mechanism of attenuation of skeletal muscle protein catabolism in cancer cachexia by eicosapentaenoic acid. Cancer Res. 2001; 61(9):3604–9. [PubMed: 11325828]
71. Whitehouse AS, Tisdale MJ. Downregulation of ubiquitin-dependent proteolysis by eicosapentaenoic acid in acute starvation. Biochem Biophys Res Commun. 2001; 285(3):598–602. [PubMed: 11453634]
72. Krzyminska-Siemaszko R, Czepulis N, Lewandowicz M, Zasadzka E, Suwalska A, Witowski J, et al. The Effect of a 12-Week Omega-3 Supplementation on Body Composition, Muscle Strength and Physical Performance in Elderly Individuals with Decreased Muscle Mass. Int J Environ Res Public Health. 2015; 12(9):10558–74. [PubMed: 26343698]
73. Couet C, Delarue J, Ritz P, Antoine JM, Lamisse F. Effect of dietary fish oil on body fat mass and basal fat oxidation in healthy adults. Int J Obes Relat Metab Disord. 1997; 21(8):637–43. [PubMed: 15481762]
74. Crochemore IC, Souza AF, de Souza AC, Rosado EL. ω-3 polyunsaturated fatty acid supplementation does not influence body composition, insulin resistance, and lipemia in women with type 2 diabetes and obesity. Nutr Clin Pract. 2012; 27(4):553–60. [PubMed: 22661243]
75. Noreen EE, Sass MJ, Crowe ML, Pabon VA, Brandauer J, Averill LK. Effects of supplemental fish oil on resting metabolic rate, body composition, and salivary cortisol in healthy adults. J Int Soc Sports Nutr. 2010; 7:31. [PubMed: 20932294]
76. Logan SL, Spriet LL. Omega-3 Fatty Acid Supplementation for 12 Weeks Increases Resting and Exercise Metabolic Rate in Healthy Community-Dwelling Older Females. PLoS ONE. 2015; 10(12):e0144828. [PubMed: 26679702]
77. Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D. Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr. 2002; 76(2):378–83. [PubMed: 12145010]
78••. Smith GI, Julliand S, Reeds DN, Sinacore DR, Klein S, Mittendorfer B. Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. Am J Clin Nutr. 2015; 102(1):115–22. This study utilized a randomized, double-blind design to convincingly demonstrate that EPA and DHA administration increases muscle volume and strength in healthy, older adults. [PubMed: 25994567]
79. Morse CI, Thom JM, Mian OS, Muirhead A, Birch KM, Narici MV. Muscle strength, volume and activation following 12-month resistance training in 70-year-old males. Eur J Appl Physiol. 2005; 95(2–3):197–204. [PubMed: 16003538]

80. Tracy BL, Ivey FM, Hurlbut D, Martel GF, Lemmer JT, Siegel EL, et al. Muscle quality. II. Effects Of strength training in 65- to 75-yr-old men and women. J Appl Physiol. 1999; 86(1):195–201. [PubMed: 9887131]

81. Roth SM, Ivey FM, Martel GF, Lemmer JT, Hurlbut DE, Siegel EL, et al. Muscle size responses to strength training in young and older men and women. J Am Geriatr Soc. 2001; 49(11):1428–33. [PubMed: 11890579]

82. Robinson SM, Jameson KA, Batelaan SF, Martin HJ, Syddall HE, Dennison EM, et al. Diet and its relationship with grip strength in community-dwelling older men and women: the Hertfordshire cohort study. J Am Geriatr Soc. 2008; 56(1):84–90. [PubMed: 18005355]

83. Reinders I, Song X, Visser M, Eiriksdottir G, Gudnason V, Sigurdsson S, et al. Plasma phospholipid PUFAs are associated with greater muscle and knee extension strength but not with changes in muscle parameters in older adults. J Nutr. 2015; 145(1):105–12. [PubMed: 25355842]

84. Rousseau JH, Kleppinger A, Kenny AM. Self-reported dietary intake of omega-3 fatty acids and association with bone and lower extremity function. J Am Geriatr Soc. 2009; 57(10):1781–8. [PubMed: 18759757]

85. Rodacki CL, Rodacki AL, Pereira G, Naliwaiko K, Coelho I, Pequito D, et al. Fish-oil supplementation enhances the effects of strength training in elderly women. Am J Clin Nutr. 2012; 95(2):428–36. [PubMed: 22218156]

86. Lewis EJ, Radonic PW, Wolever TM, Wells GD. 21 days of mammalian omega-3 fatty acid supplementation improves aspects of neuromuscular function and performance in male athletes compared to olive oil placebo. J Int Soc Sports Nutr. 2015; 12:28. [PubMed: 26085822]