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Camille Doussat, Thomas Brioche, François Casas, Frédéric Capel, Christine Feillet-Coudray

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REVIEW OPEN ACCESS

Dietary omega 3 fatty acids and skeletal muscle metabolism: a review of clinical and preclinical studies

Camille Doussat[1], Thomas Brioche[1], François Casas[1], Fréderic Capel[2] and Christine Feillet-Coudray[1,*]

[1] DMEM, Univ Montpellier, INRAE Montpellier, France
[2] UMR1019 Unité de Nutrition Humaine (UNH), INRAE, Université Clermont Auvergne, Clermont-Ferrand, France

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Abstract – *Background*: There is a myriad of metabolic roles of omega-3 fatty acids. More recently, studies have looked at omega-3 fatty acids effects on skeletal muscle. *Objectives*: The objective was to determine their effects in situations such as physical activity, obesity, sarcopenia and cachexia. Methods: Bibliographic searches focused on the PubMed database, looking in priority at systematic reviews, until November 2023. Twenty-seven papers were finally included. *Results*: Omega-3 fatty acids could increase protein anabolism, reduce protein catabolism in the context of exercise-related muscle damages, and could induce beneficial mitochondrial modifications. In obesity, omega-3 fatty acids participate in weight loss and its maintenance, and can help decrease insulin resistance. In sarcopenia atrophic conditions, omega 3 fatty acids allow muscle mass and function maintenance. In cancer cachexia, omega 3 fatty acids are more efficient at the pre-cachectic stage, as they can reduce protein catabolism and increase protein anabolism, but cannot reverse energy imbalance. *Conclusions*: Omega 3 fatty acids have multiple beneficial effects on skeletal muscle in physical activity, obesity, sarcopenia and cachexia. Yet, these effects are mediated by EPA and DHA, whose sources are solely of marine origins. As marine resources are overexploited, finding diverse sources of omega-3 fatty acids is crucial.

Keywords: Omega 3 fatty acids / skeletal muscle / physical activity / obesity / sarcopenia / cachexia

Résumé – *Contexte* : Les acides gras oméga 3 possèdent de nombreuses propriétés métaboliques. Récemment, plusieurs études ont considéré leur action sur le muscle squelettique. *Objectifs* : L'objectif de cette revue est d'analyser leurs effets dans des situations telles que l'activité physique, l'obésité, la sarcopénie et la cachexie. *Méthodes* : Les recherches bibliographiques ont porté sur la base de données PubMed, en examinant en priorité les revues systématiques, ceci jusqu'en novembre 2023. Vingt-sept articles ont été inclus. *Résultats* : Les acides gras oméga-3 augmenteraient l'anabolisme et diminuerait le catabolisme des protéines, dans un contexte de dommages musculaires liés à l'exercice, et induiraient des modifications mitochondriales bénéfiques. Dans l'obésité, ils favoriseraient la perte de poids et son maintien, et aideraient à diminuer la résistance à l'insuline. Dans la sarcopénie, ils permettraient un maintien de la masse et de la fonction musculaire. Dans la cachexie cancéreuse, les acides gras oméga-3 seraient plus efficaces au stade pré-cachectique, en modulant le métabolisme protéique, mais cependant ils n'inverseraient pas le déséquilibre énergétique. *Conclusions* : Les acides gras oméga 3 ont de multiples effets bénéfiques sur le muscle squelettique dans un contexte d'activité physique et d'obésité, lors de la sarcopénie et de la cachexie. Cependant, ces effets sont médiés par l'EPA et le DHA, dont les sources sont uniquement d'origine marine. Les ressources marines étant surexploitées, il est crucial de trouver des sources diversifiées d'acides gras oméga-3.

Mots clés : Aides gras oméga 3 / muscle squelettique / activité physique / obésité / sarcopénie / cachexie

* Corresponding author: christine.coudray@inrae.fr

Highlights

- Omega-3 fatty acids have multiple beneficial effects on skeletal muscle
- EPA and DHA, whose sources are exclusively marine, mediate these effects
- Finding diverse sources of omega-3 fatty acids is essential, as marine ressources are overexploited

1 Introduction

The multiple metabolic roles of omega-3 fatty acids are well known. Their major effects are their anti-inflammatory action through their metabolites involved in resolving inflammation, and their competition with omega-6 fatty acids, pro-inflammatory molecules (Gammone *et al.*, 2018). In addition, they are thought to play a role in the prevention of cardiovascular disease by lowering blood triglycerides, increasing high density lipoprotein (HDL) concentration and decreasing platelet aggregation (Jeromson *et al.*, 2015). At the same time, their effects on muscle have been studied and these effects seems of particular interest in various pathophysiological situations such as physical activity, obesity, sarcopenia and cachexia. This review aims to give a brief overview of the current knowledge regarding the effect of dietary omega 3 effect on skeletal muscle. After a brief overview of omega-3 fatty acid metabolism, we will discuss the potential mechanisms through which these fatty acids could enhance physical activity and sports performance. Additionally, we will examine their role in the prevention of certain metabolic disorders linked to obesity, as well as their potential to prevent the loss of muscle mass and function during aging and in cancer.

2 Method

Bibliographic searches focused on the PubMed database. Keywords were "omega 3 OR *n* 3 PUFA AND skeletal muscle"; "omega 3 OR *n* 3 PUFA AND skeletal muscle AND obesity"; "omega 3 OR *n* 3 PUFA AND cancer cachexia"; "omega 3 AND obesity" with a publication date restriction between 2002 and November 2023. Priority was given to systematic reviews and publications explaining the mechanics of the actions. They were only included if they studied the metabolic effects of omega 3 on skeletal muscle, particularly in the fields of sport, obesity, sarcopenia or cachexia. Twenty-seven papers were finally included.

Some recalls about omega 3

The precursor of the group of omega-3 fatty acids is alpha-linolenic acid (ALA), synthesized only by plants, which makes it essential in the human diet. ALA is metabolized in human body by elongases and desaturases leading to the formation of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) (Jeromson *et al.*, 2015). More specifically, alpha-linolenic acid is converted to EPA by elongation of the fatty acyl chain and insertion of two additional double bonds into it. EPA is further metabolised to DHA through a complex set of reactions involving chain elongation, desaturation (insertion of a double bond) and partial oxidation. Desaturation and elongation reactions occurs in the endoplasmic reticulum and are followed by a final peroximal beta-oxidation process (Videla*et al.*, 2022). Delta-6 desaturase and delta-5 desaturase catalyse the formation of a double bound in the 6th and the 5th carbon from the carboxylic end, respectively (Videla *et al.*, 2022), the two-carbon elongation are carried out by elongases 2 and 5, whereas beta-oxidation leads to the production of DHA. According to a recent study conducted in mice by Valenzuela *et al.* (2024), liver have the highest capacity for PUFA biosynthesis, while activity is limited in brain, testicles, and kidney, and not detectable in heart and lung. The conversion rate of ALA to EPA in human is between 8% and 12%, while that of ALA to DHA is around 1% (Brenna, 2002). In a number of diseases associated to oxidative stress, including overnutrition-induced obesity that leads to non-alcoholic fatty liver disease, a drastic lowering in the hepatic activity of delta-5 desaturase and delta-6 desaturase is observed, as a consequence of oxidative stress. This leads to a depletion of omega-3 fatty acids in the liver, with a negative impact on their systemic abundance (Videla *et al.*, 2022).

Dietary sources of omega-3 are various. ALA is found mainly in plant foods, such as walnuts and walnut oil, flaxseed and flaxseed oil, chia seeds, soybeans, rapeseed oil and seaweed. ALA is also found in animal products when animals consume plant sources of ALA. EPA or DHA are exclusively of marine origin: fish, especially oily fish such as mackerel, sardines and herring, as well as seaweed.

According to the French Agency for Food, Environmental and Occupational Health Safety (ANSES 2016), daily adequate intake are 250 mg for EPA, 250 mg for DHA, and 1% of total daily energy intake for ALA. The French National Nutrition and Health Program (PNNS) 4 recommends eating two portions of fish per week, including one of oily fish, and encourages consumption of rapeseed or walnut oil.

EPA and DHA are metabolically more active than ALA which is then mainly considered as a precursor of EPA and DHA. Indeed, oxylipins including resolvins, protectins and maresins, are produced from EPA and DHA by cyclooxygenases, lipoxygenases and cytochrome P450 (Albracht-Schulte et al., 2018). Other metabolites, such as endocannabinoids, are also derived from EPA and DHA (D'Angelo et al., 2020).

3 Physical activity and sport

During exercise, muscles are solicited in different ways depending on the discipline practiced. In particular, some disciplines require muscle mass gain such as weight lifting and throwing sports.

Several studies have shown that omega-3 fatty acids have anabolic effects (Jeromson *et al.*, 2015) by increasing muscle protein synthesis through the activation of mTOR (Gammone *et al.*, 2018) or p70s6k and mTOR (Albracht-Schulte *et al.*, 2018; Jeromson *et al.*, 2015). The benefits are all the more ostensible when an inflammatory state exists, for example during recovery from intense physical exercise such as eccentric contraction exercises, thanks to the restoration of the Akt/mTOR/FoxO3 signalling pathway (Jannas-Vela *et al.*, 2023). However, while some studies have concluded an increase in muscle mass (Gammone *et al.*, 2018), other did not found that increased muscle protein synthesis resulted in net muscle gain (Albracht-Schulte *et al.*, 2018).

In addition, omega-3 fatty acids may reduce protein catabolism (Jeromson *et al.*, 2015). Anti-inflammatory action is a main property of omega 3 fatty acids, thus they prevent protein degradation due to inflammation (Gammone *et al.*, 2018). EPA supplementation has been shown to inhibit the transcription factor NF-kappa B, involved in the regulation of immunity and inflammation, and notably in the increase in protein degradation in inflammatory states (Jeromson *et al.*, 2015) and it down-regulates proteasome expression involved in protein degradation (Huang *et al.*, 2020). In addition, omega-3 fatty acids decrease circulating level of cortisol, a known activator of protein catabolism (Albracht-Schulte *et al.*, 2018).

Exercise induced muscle damages, resulting in transient muscle inflammation, strength loss, muscle soreness and may cause subsequent exercise avoidance (Clarkson *et al.*, 2002). Omega-3 fatty acids have been shown to be beneficial for muscle recovery, both *in vitro* and in animals or humans (Jannas-Vela *et al.*, 2023). In fact, by contributing to the resolution of inflammation, omega-3 fatty acids enable faster healing of muscle lesions (Jannas-Vela *et al.*, 2023). Feelings of fatigue and soreness could also be reduced by a high efficiency of the repair process with a reduction in markers of muscle damage (Gammone *et al.*, 2018).

It is likely that the beneficial effects of omega-3 fatty acids arise from their incorporation into cell membranes (Macartney *et al.*, 2019), as omega-3 fatty acids in phospholipid form have better bioavailability for metabolic pathways than in triglyceride form (Jeromson *et al.*, 2015). Indeed, EPA and DHA from cell membranes can be better extracted for metabolism, like omega-6 fatty acids (Jannas-Vela *et al.*, 2023). In rats, DHA is predominantly incorporated into the cell membranes of fast-type muscle fibers, and muscle fibers with a more oxygen-poor environment (Macartney *et al.*, 2019). Thus integrated into cell membranes, omega-3 fatty acids contribute to membrane fluidity, promoting endocytosis and exocytosis. They also alter lipid rafts which can modify their function and activity, interfering with ion channels to regulate their activity (Kalupahana *et al.*, 2020).

In addition, omega-3 fatty acids also improve muscle strength (Huang *et al.*, 2020; Gammone *et al.*, 2018). DHA participates in better conduction of action potentials, which improves the number of motor units recruited for a movement and therefore the force deployed (Gammone *et al.*, 2018).

Systematic review and meta-analysis of the literature have led to the conclusion that an effect of omega 3 FA on muscle mass and strength exist (Abdelhamid *et al.*, 2019; Rondanelli *et al.*, 2021; Bird *et al.*, 2021). However, it seems that the strength of the studies is rather low and that high quality randomized controlled trial are still required to validate the conclusions (Abdelhamid *et al.*, 2019; Bird *et al.*, 2021).

The actions of omega-3 fatty acids on mitochondria have also been reported. Notably, EPA promotes mitochondrial biogenesis (Kalupahana *et al.*, 2020). Furthermore, EPA protects mitochondrial proteins while DHA induces an increase in mitochondrial mass, and the two influence mitochondrial fusion both *in vitro* and *in vivo* (Chen *et al.*, 2018). In rats, fish oil rich in EPA and DHA increases mitochondrial fusion and reduces fission (Chen *et al.*, 2018). DHA may even reverse the negative effects of palmitate, a saturated fatty acid, on mitochondrial fragmentation (Macartney *et al.*, 2019). Thus omega-3 fatty acids increase mitochondrial synthesis (Albracht-Schulte *et al.*, 2018) by increasing mRNA transcription (Jeromson *et al.*, 2015).

In addition, omega-3 fatty acids promote lipid beta-oxidation in mitochondria, probably through activation of PPARα (Albracht-Schulte *et al.*, 2018). Similarly, EPA and DHA, by activating AMPK, increase lipid oxidation (D'Angelo *et al.*, 2020). EPA is catabolized more often than DHA (D'Angelo *et al.*, 2020).

In summary, numerous studies show that omega-3 fatty acids increase protein anabolism and reduce protein catabolism in the context of exercise-related muscle damages. They could also increase muscular strength by acting on the nervous system and induce beneficial mitochondrial modifications.

4 Obesity

Obesity greatly increases the risk of developing various metabolic and cardiovascular pathologies, such as type 2 diabetes, atherosclerosis and high blood pressure. Weight loss is often difficult, and weight is easily regained later, because most obese individuals have little muscle mass, which is largely responsible for basal energy expenditure, while fat mass consumes little energy (Axelrod *et al.*, 2023). Thus, the benefit of gaining muscle mass would be to increase basal metabolism, enabling longer-lasting weight loss.

Animal studies show that omega-3 fatty acids supplementation improves weight loss, insulin sensitivity and the resolution of inflammation (Kalupahana *et al.*, 2020). However, these effects are not consistent in human studies (Kalupahana *et al.*, 2020). Thus, some studies observe in humans, with omega-3 fatty acids supplementation, a significant increase in muscle mass gain, but the majority see no effect on muscle mass (Albracht-Schulte *et al.*, 2018), or on weight loss (Kalupahana *et al.*, 2020).

On the other hand, while omega-3 fatty acids do not significantly influence weight loss, they do potentiate the effects of a restrictive diet, even at low doses (Albracht-Schulte *et al.*, 2018). What's more, omega-3 fatty acids could help maintain weight loss (Kalupahana *et al.*, 2020). Indeed, weight gain following weight loss is often due to a drop in leptin levels leading to increased hunger, yet EPA regulates leptin levels, helping to stabilize hunger and weight (Kalupahana *et al.*, 2020). In mice, adequate omega-3 intakes during pregnancy and the first months of life appear to prevent obesity through the absence of adipocyte hypertrophy (Kalupahana *et al.*, 2020). In humans, adequate omega-3 fatty acids intakes during

pregnancy and the first months of life reduce the percentage of fat mass in childhood (Kalupahana *et al.*, 2020).

Omega-3 fatty acids are also thought to have beneficial effects against the metabolic disorders associated with obesity. For example, they can improve insulin sensitivity, fatty acids oxidation and glucose tolerance (Gammone *et al.*, 2018; Pinel *et al.*, 2015), by increasing the expression of the glucose transporters GLUT1 and GLUT4 (Jeromson *et al.*, 2015). In addition, EPA improves glucose uptake by cells, independently of Akt, a protein kinase involved in the insulin signaling pathway (Jeromson *et al.*, 2015). Regarding insulin sensitivity, omega-3 intakes are inversely correlated with insulin resistance (Kalupahana *et al.*, 2020). However, they are not able to improve it when it is already established, only to partially reduce it in adipose tissue via their anti-inflammatory action (Kalupahana *et al.*, 2020).

5 Sarcopenia

Sarcopenia is the loss of muscle mass that occurs naturally with age. Omega-3 fatty acids can slow the loss of muscle mass (Jeromson *et al.*, 2015). Indeed, by resorbing inflammation (Gammone *et al.*, 2018) or influencing proteasome expression (Huang *et al.*, 2020), omega-3 fatty acids decrease protein catabolism (Deval *et al.*, 2016). EPA and DHA are both responsible for these actions (Vega *et al.*, 2021). At 2 g/day, omega-3 fatty acids show measured results on muscle mass gain for elderly populations, and the magnitude of the benefit increases with higher doses (Huang *et al.*, 2020). Omega-3 fatty acids could prevent the onset of sarcopenia (Gammone *et al.*, 2018) when provided over the long term (Vega *et al.*, 2021). It has also been demonstrated that EPA and DHA could increase muscle protein synthesis and muscle function in older adults (Smith *et al.*, 2011, 2015). However, these results are controversial, since a meta-analysis reports no benefit of omega-3 fatty acids on muscle mass (Cornish *et al.*, 2022). It should be noted that the inflammatory status of the subject was not taken into account in the latter. In subjects without low-grade inflammation, omega-3 fatty acid supplementation may be useless.

However, the European Sarcopenia Working Group EGWSOP has redefined sarcopenia to include loss of muscle strength (Cruz-Jentoft *et al.*, 2019). The actions of omega-3 fatty acids on muscle strength are not significant at 2 g/day (Huang *et al.*, 2020). Nevertheless, omega-3 fatty acids potentiate strength training-related improvements in muscle strength, possibly by increasing muscle sensitivity to acetylcholine, the neurotransmitter of muscle contraction (Jeromson *et al.*, 2015). They may also improve information conduction along axons (Cornish *et al.*, 2022). This benefit is of particular interest since decreased motor unit recruitment generally precedes loss of muscle function (Jeromson *et al.*, 2015). In addition, an omega-3 fatty acids deficiency affects synaptic plasticity (D'Angelo *et al.*, 2020). Finally, at very high doses (>3 g/d), omega-3 fatty acids alone are sufficient to maintain muscle mass and strength (Jeromson *et al.*, 2015).

Thus, in conditions of muscle atrophy during aging, omega-3 fatty acids manage to maintain muscle mass and function, the effect for which they are most effective (Jeromson *et al.*, 2015; Deval *et al.*, 2016).

6 Cachexia

Cancer cachexia is a complication of cancer, consisting of loss of both fat and lean body mass associated with loss of appetite (Jin *et al.*, 2022), in the presence of an inflammatory syndrome (Braha *et al.*, 2022). Conclusions on the effects of omega-3 fatty acids on cancer cachexia are limited and controversial, but suggest that anti-inflammatory, anti-catabolic and anti-lipolytic properties are beneficial in the treatment of cancer cachexia (Freitas and Campos, 2019).

Half of clinical studies conclude that omega-3 fatty acids do not improve patients' weight or muscle mass (Freitas and Campos, 2019; Braha *et al.*, 2022; Jin *et al.*, 2022). Omega-3 fatty acids nevertheless show benefits in terms of quality of life and patient survival (Jin *et al.*, 2022; Freitas and Campos, 2019).

The other half of studies show that omega-3 fatty acids are able to halt weight loss (Jin *et al.*, 2022), or even allow weight regain (Braha *et al.*, 2022). Omega-3 fatty acids combined in different supplements also produce positive results on weight gain, although it is not possible to determine how much is due to omega-3 fatty acids and how much to other components (Mochamat *et al.*, 2016). Finally, omega-3 fatty acids enable greater weight gain than a placebo, demonstrating their validity in the treatment of cachexia, albeit less effectively than conventional megestrol acetate treatment (Harvie, 2014).

The beneficial effects of omega-3 fatty acids are explained by several mechanisms. Firstly, reduced systemic inflammation decreases inflammation-induced protein catabolism (Jin *et al.*, 2022). EPA also acts by decreasing protein degradation (Braha *et al.*, 2022), thus inhibiting the muscle atrophy of cachexia (Harvie, 2014). EPA also inhibits ubiquitin signaling of proteasomes, reducing protein degradation (Jeromson *et al.*, 2015).

Lastly, an effect of omega-3 fatty acids that is ancillary to muscle but important in the treatment of cancer cachexia is the reduction of medical anorexia (Vega *et al.*, 2021).

The hypotheses put forward to explain the lack of action of omega-3 fatty acids in half the studies is the fact that significant weight loss in cachexia is largely due to loss of appetite; thus, energy intakes remain low despite high requirements (Jin *et al.*, 2022). However, omega-3 supplementation provides a few grams of lipids which, although calorific, do not restore the balance between intake and expenditure (Jin *et al.*, 2022). The effects of omega-3 fatty acids would therefore be existing but insufficient to be detected clinically, or to significantly improve patients (Jin *et al.*, 2022). Recently, it has been found that DHA could prevent cancer cell escape from immune surveillance and be a tool in the prevention of malignancy (Zhang *et al.*, 2023) and the development of cachexia.

For these reasons, in 2017, the European Society for Clinical Nutrition and Metabolism (ESPEN) included omega-3 fatty acids in the treatment recommendations for cancer cachexia (Freitas and Campos, 2019). However, omega-3 fatty acids supplementation is thought to be more effective if started at the pre-cachectic stage, in order to protect muscles from excessive catabolism without being hampered by the imbalance in energy balance (Jin *et al.*, 2022).

7 Conclusion

Compendiously, in addition to their well-known anti-inflammatory and cardiovascular health properties, omega-3 fatty acids could prevent muscle catabolism and increase anabolism. In this sense, they are useful for athletes to combat the resistance to anabolism that can appear and hinder muscle mass gain, but also for the elderly in prevention and as a complement to treatment for sarcopenia, as well as for patients at risk of cancer cachexia to protect their muscle mass. With regard to obesity, the effects of omega-3 fatty acids are also beneficial directly on muscle mass gain or indirectly by reducing insulin resistance.

The multiple beneficial effects on skeletal muscle described in this review can be achieved with a diet that provides omega-3 fatty acids (fish and shellfish) and directly with dietary supplementation. In France, the foods that contribute to omega-3 fatty acids intake are rapeseed oil, walnuts and walnut oil, and fish, shellfish and crustaceans, but only seafood provides EPA and DHA. Yet global warming could reduce the omega-3 content of algae, affecting the entire marine food chain (Jeromson *et al.*, 2015). What's more, at their current rate of exploitation, fishery resources are dwindling. This is why various species of algae, krill, plankton but also sponges, fungi and bacteria are currently being studied as alternative sources of EPA and DHA, with the aim of being widely exploited and commercialized (Gammone *et al.*, 2018). Thus, the challenge for the coming years is to develop and secure sustainable sources of omega 3 for the future.

Conflicts of interest

The authors declare no competing interest.

Author contribution statement

All the authors wrote the paper and approved the final version of this manuscript.

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