Omega 3 fatty acids as nutraceuticals in sporting performances

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Abstract— **It is now known an increased oxidative stress and inflammatory responses among individuals performing strenuous exercise. In addition, it is known that exhaustive and/or unaccustomed exercise can lead to muscle fatigue, delayed onset muscle soreness, and a decrement in performance. Omega-3 polyunsaturated fatty acids (ω3PUFAs) have been shown to decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species, to possess immunomodulatory effects, and to attenuate inflammatory diseases. Although, a number of studies have assessed the efficacy of ω3PUFA supplementation on red blood cell deformability, muscle damage, inflammation, and metabolism during exercise, only a few studies have evaluated the impact of ω3PUFA supplementation on exercise performance. The purpose of this review is to examine the evidence regarding the potential of ω3FA supplementation for positively impacting the physiological response to exercise. In particular, this review will evaluate the efficacy of ω3FA supplementation on exercise-induced muscle damage and inflammation, exercise metabolism, exercise performance (including muscular and aerobic adaptations) in humans. This review demonstrates that, at present, we cannot conclude the hypothesis that ω3PUFA supplementation is effective and ergogenic, and that the data is inconclusive whether ω3PUFA supplementation effectively attenuates the inflammatory and immunomodulatory response to exercise. Future human studies should assess the effectiveness of ω3PUFA supplementation on delayed onset muscle soreness, and subsequent exercise performance, in multisport athletes who typically engage in more than one bout of exercise per day, using a more robust research design than those that have been used in previous studies.**

Index Terms— **Essential fatty acid, nutraceuticals, omega 3, polyphenols, physical performance.**

I. INTRODUCTION

There is an increasing interest in finding nutrients and supplements that can improve athletic performance and recovery. Athletes often use dietary supplements in order to increase metabolic capacity, delay fatigue onset, improve muscle hypertrophy, and shorten recovery periods. In addition, athletes can often face a reduction in immune function, due to intense exercise training and a frequent challenging competition, which becomes more prone to upper respiratory tract infections. Exercise training exerts a physiologic stress on the body, which requires a coordinated response by the cardiovascular, pulmonary, and nervous systems to increase the blood flow and the oxygen supply to the working skeletal muscle. At rest, muscle receives approximately 20% of the total blood flow, but, during exercise, this can increase to more than 80% [1].

In recent times the concept of the presence, in daily consumption foods, of *nutraceutical* components is born; these are food components, called "functional", which provide important benefits for human health, not only in conservative terms, but above all preventive. Many nutraceuticals derive from vegetables, plant extracts, as phytochemicals, containing secondary metabolites have served as anti-oxidants in phytotherapeutic medicines to protect against various diseases for centuries [2]-[3]. The largest number of nutraceuticals belong to the polyphenol group: natural phenolic substances are secondary plant metabolites, a major group of plant compounds (over 8000) chemically characterized by the presence of one or more aromatic rings with one or more hydroxyl substituents [4]. These phytochemicals are structurally diverse, and include flavonoids, phenolic acids, stilbenes and lignans [5]. Polyphenols possess anti-oxidant [6]-[7] and anti-proliferative actions [8]-[9], but also a wide range of beneficial effects against atherosclerosis, brain dysfunction, stroke, cardiovascular diseases, and cancer [11]-[12]-[13]-[14]. Therefore, among the foods related to nutraceuticals there are above all fruit and vegetables, rich in antioxidants. Leutin, useful for sight, is found in spinach, cabbage, broccoli and eggs. Curcumin in the curry and yellow saffron pigment. Isoflavones are present in legumes. Brewer's yeast contains amino acids, carbohydrates, proteins, mineral salts and vitamins. In the bark of the maritime pine we find the pycnogenol, useful for the prevention of cardiovascular diseases and dermal diseases. Resveratol is present in the grape skin and in the wine. In tea, theanine and theine. carotenoids, folic acid, melatonin, carnitine. In Table 1 some *nutraceuticals* present in food are reported. Omega 3 fatty acids (PUFAs) are also considered *nutraceuticals* and various studies in recent years have shown the beneficial effects of ω-3 poly unsaturated fatty acids through diverse mechanisms including anti-oxidant and anti-inflammatory effects.

II. OMEGA 3: BENEFITS AND PROPERTIES

Ergogenic aids can help prepare an individual to exercise, improve exercise efficiency, improve recovery from exercise or help prevent injury during intense training. In this regard, Omega-3 has recently been considered an ergogenic supplement, which can play a role in these processes, which not only counteract the inflammation induced by exercise, but also improve muscle health and its availability of energy. Omega-3 fatty acids are a type of polyunsaturated fats considered essential because the human organism is not able to synthesize them in sufficient quantities to satisfy its needs. Their properties, in contrast to those of Omega-6 fatty acids, are associated with beneficial effects on the health of the cardiovascular system and the nervous system, and not only: years of studies demonstrate their potential usefulness also against diseases that affect other organs and systems. To meet the needs of ω-3 it is first of all possible to rely on nutrition.

Classification

Fatty acids are classified according to their different degree of saturation in three main classes:

- saturated fatty acids (SFA)
- monounsaturated fatty acids (MUFA)
- polyunsaturated fatty acids (PUFA)

SFAs have a simple carbon chain that does not contain double bonds, MUFAs have a carbon chain with a double bond and PUFAs are classified as carbon chains containing two or more double bonds. The differences in the chemical structure of these different classes can determine different physiological effects. For example, SFAs have been linked to the development of metabolic dysfunction, while on the contrary some MUFA and PUFA have positive effects on metabolic function. At the cellular level, fatty acids are not only structurally important, as the main component of cell membranes, but they also have an important function in a number of metabolic processes, such as the regulation of the activity of certain enzymes and acting as signal molecules. Therefore, alterations in the composition of the muscle lipid pool can have profound effects on the metabolic and physical function of skeletal muscle. It is known that skeletal muscle is sensitive to changes in lipids introduced with the diet: a minimum change of 2 weeks in dietary intake is sufficient to significantly alter the muscle lipid composition [15].

The fatty acids defined as Omega 3 are called polyunsaturated since they have different unsaturations along the chain, that is they have a variable number of double bonds and are defined Omega-3 for a double bond to the third carbon from the methyl end of the carbon chain (Figure 1).

Humans do not possess the Omega-3 desaturase necessary to add a double bond to the 15th carbon of a long chain fatty acid and, therefore, are unable to synthesize alpha-linoleic acid (ALA 18: 3n-3) and linoleic acid (LA 18: 2n-6) making them essential fatty acids. Omega-6 PUFAs are also essential fatty acids and generally have metabolically distinct effects compared to Omega-3 PUFAs. While the human body cannot synthesize Omega-3 and Omega-6 PUFAs, it has the ability to further metabolize these fatty acids through phases of elongation and desaturation.

It is thought that hominid diets during the Paleolithic were high in seafood and poor in vegetable seeds and oils, which led to an Omega-6/Omega-3 ratio of about 1:1. Therefore, given the probability that the diets of the first human ancestors were characterized by a high intake of Omega 3, the endogenous ability to synthesize the Omega-3 PUFAs may not have conferred any developmental advantage to development. But, during the agricultural revolution, with changes in food production in the Neolithic era, this n-6/n-3 relationship began to diverge. In the current typical Western diet, this ratio is thought to be 20:1, with the intake of Omega-3 PUFA predominantly from ALA. Although unlikely to be a primary driver; the divergence in the n-6/n-3 relationship occurred in conjunction with the increase in cardiovascular disease and chronic inflammation states.

In short, Omega-6 PUFAs are associated with the production of pro-inflammatory mediators, while Omega-3 PUFAs produce less powerful inflammatory mediators and inflammatory resolving proteins and therefore controlling this ratio can lead to positive health outcomes. [15].

ALA can be metabolized to eicosapentaenoic acid (EPA 20: 5 n-3) and docosahexaenoic acid (DHA 22: 6n-3) of Δ6 desaturase and Δ5 desaturase respectively, while LA is converted to arachidonic acid (AA 22: 4n- 6). However, the conversion of ALA to DHA is very inefficient with a conversion <10% in females and <3% in males. While ALA is the preferred substrate for Δ6 desaturase, an abundance of food linoleic acid has been shown to suppress the conversion of ALA in DHA, which could be a confounding factor in these studies (Figure 1)

The main Omega-3 fatty acids are:

- α-linolenic acid 18: 3 (precursor Omega 3)
- eicosapentaenoic acid (EPA) 20: 5
- docosahexaenoic acid (DHA) 22: 6.

The first number indicates the carbon atoms of the chain, the second the number of double bonds present. With precision the unsaturations of these fatty acids are of the cis type, ie the hydrogen atoms are on the same side of the plane. For this reason the Omega-3 molecule seen under the microscope will appear with a helical shape. These fats are defined as essential, since the body cannot synthesize them but only take them with the diet. However, it is possible to produce small amounts of EPA and DHA starting from their precursor, α-linolenic acid. For this reason it is essential to follow a diet rich in ω-3, otherwise the body alone with the use of precursors fails to reach the in quantity necessary to satisfy primary needs.

EPA: Eicosapentaenoic acid

The EPA is an essential fatty acid formed by a chain of 20 carbon atoms with 5 double bonds, therefore polyunsaturated, from the ω–3 family. It is present mainly in microalgae, both fresh and salt water, and accumulates in the meat of fish that feed on phytoplankton. In particular, the fish that live in cold sea waters such as cod, tuna, mackerel, salmon, herring, sardines and blue fish in general are richer. The EPA is also found in breast milk and in the oil obtained from the fish mentioned above. It is not present in freshwater fish species. Vegetarians can take this essential fatty acid from algae such as spirulina and klamath algae. In some oil seeds we find alpha linolenic acid, which although with some difficulty, can be converted by the body into eicosapentaenoic acid.

The main function performed is the anti-inflammatory one. In particular circumstances it is subjected to a series of enzymatic reactions that generate molecules called good eicosanoids, which counteract the pro-inflammatory activity together with the molecules derived from arachidonic acid (AA). EPA and AA are placed together in the phospholipid layer of the cell membrane regulating the entry and exit of cellular metabolites.

DHA: Docosahexaenoic acid

DHA is an essential fatty acid formed by a chain of 22 carbon atoms on which 6 unsaturations are present. It too belongs to the Omega 3 family. It is present in fairly large quantities in fish, particularly salmon, mackerel, sardines, herring, tuna and anchovies. As for the EPA, the oils obtained from these fish are particularly rich. Other foods in which it is possible to find it are the flax seeds and in the eggs of the oviparous (hens). DHA is also present in breast milk but not in the vaccine and its derivatives. For this reason, in recent years the practice of supplementing the diet of pregnant women with DHA supplements has been introduced, so as to ensure the correct development of brain tissue in children.

The ω–3 perform mainly three functions:

1. anti-platelet aggregation action, or reduce the possibility of forming blood clots
2. control of lipid concentration, in particular of triglycerides present in the plasma
3. control of arterial pressure, making the walls of arteries elastic and fluid the cell membranes

The potential therapeutic benefit of a diet with high Omega-3 content has been observed in Greenland Inuit populations with the lowest incidence of CVD. In fact, the discovery of the effects of Omega 3 on health dates back to about forty years ago, in the 1970s. American researchers studied the health status of the Inuit, the Eskimo populations living at the Arctic Circle, in Alaska, Canada and Greenland.

Positive action of Omega 3 on the Inuit

The term Eschimesi indicates those belonging to an indigenous population that resides mainly on the Arctic coasts of North America, in Greenland and in Asia at the extremity of the Ciukci peninsula. The Eskimo appellation was coined by another native American population, the Algonquins of eastern Canada, meaning "raw meat eaters". However, the Eskimos do not like the use of this name because they have their own specific name that identifies them, namely Inuit, which means "man".

In the winter of 1976 an examination of the composition of Eskimo food was carried out in northwestern Greenland. Duplicate samples of diets collected from 50 adults, males and females were analyzed: water, proteins, fats, cholesterol and carbohydrates. The results were compared with those of typical Danish diets. Seals and fish represent the pre-dominant Eskimo food. Marked differences were found between Eskimo and Danish food. The Eskimo diets were richer in polyunsaturated fatty acids, the ratio to saturated fatty acids was 0.84 compared to 0.24 Danes. The polyunsaturated fatty acids were predominantly of the linolenic class (n-3) in the Eskimos and in the linoleic class (n-6) in the Danes. The rarity of ischemic heart disease in Greenland Eskimos can be partially explained by the antithrombotic effect of long chain polyunsaturated fatty acids, in particular the eicosapentaenoic acid prevalent in diets rich in marine oils [16].

The results astonished the scientists, who, considering the particularly rich diet of fats of these populations, imagined to run into big cardiovascular problems. On the contrary, the Inuit had an efficient cardiac function and in general an excellent state of health. Making several analyzes it was very clear that the diseases related to the heart and to the circulatory system had a very low incidence, correlated therefore to the type of feeding followed. On this trail, the protective role and the possible mechanism of action of unsaturated fats of marine animals has led to a tendency towards a diet that involves the consumption of fatty fish, especially salmon and bluefish. However, fish is an important food in the diet, also due to the richness of other precious nutrients including selenium, iodine, zinc, calcium and protein.

The natives of Greenland, the Inuit, have lived for a long time in extreme conditions in the Arctic, including low annual temperatures, and with a special diet rich in proteins and fats, in particular ω-3 polyunsaturated fatty acids (PUFA). In addition to whale and seal meat, the Inuit consume large quantities of fish, whose oil is rich in Omega 3 fatty acids. Despite a traditional diet very low in fruit and vegetables and rich in animal fats, the Inuit are generally in good health, presenting a low incidence of cardiovascular diseases, already observed by Danish researchers in the 70s.

The Inuit genome was analyzed and then compared with that of other peoples. The genomes of 191 Greenlanders with less than 5% of European genes were compared with those of 60 Europeans and 44 Chinese. They discovered that, practically, all the members of this Arctic population have a cluster of mutations in the genes that control acid metabolism fats, present on the contrary in just 2% of Europeans: this would allow the Inuit to compensate for the potentially negative effects of an excess of animal fats, including Omega-3. Analyzing the membrane lipids, it was found that the selected alleles modulate the fatty acid composition, which can influence the regulation of growth hormones. Thus, the Inuit are, from a genetic point of view, adapted to a diet rich in polyunsaturated fatty acids. So ... "the evolutionary consequences of inhabiting a stimulating environment can be seen in the Inuit genome of Greenland". Scholars have found signs of selection for genetic variants in fat metabolism, not only for the proliferation of brown fat cells that produce heat, but also to cope with the large quantities of polyunsaturated fatty acids typical of their diet rich in foods from marine origin. They concluded that ω–3 should have protective effects to explain this paradox [17].

These genetic characteristics also influence the heights of the population, because growth is partly regulated by the metabolism of fats. In the Inuit, these mutations reduce their size by two centimeters. These genetic mutations date back at least 20,000 years and may have helped many human populations, such as hunter-gatherers, adapt to diets rich in animal fats and some types of Omega-3 and Omega-6 fatty acids. This genetic selection is old: it may have initially appeared in Siberians living in the Arctic and arriving in Greenland when the Inuit settled about a thousand years ago. Today at least 10% of Americans take omega-3 regularly as supplements. But the results of recent clinical studies have not confirmed the cardiovascular benefits of Omega 3 or protection against, for example, Alzheimer's disease. In fact, the Inuit have a unique genetic adaptation to this diet that cannot be extrapolated to other ethnic groups. Therefore, "the intake of abundant ω–3 is very positive for the Inuit, but not for the other Populations" [17].

Omega 3 effects

Omega-3 PUFAs are essential nutrients for normal growth and human development; they cannot be synthesized de novo by the human body, so we must rely on dietary foods to acquire them. These fatty acids can modulate physiological and pathological conditions through multiple mechanisms, such as the inflammatory response, and have received great attention in recent years for their fundamental role in disease prevention and management. Recent research shows that adequate levels of long-chain ω-3 PUFAs, especially those found in fish or fish oils, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), optimize health and prevent disease.

Today many foods common to the Western diet are deficient in ω-3, but abundant in ω-6 PUFAs, with a very high Omega-6/Omega-3 ratio. It is believed that this unbalanced relationship is associated with the modern prevalence of cardiovascular diseases, cancer, diabetes and neurodegenerative diseases, which affect millions of people around the world. Emerging evidence indicates that dietary supplementation with ω-3 PUFA may reduce the risk of these diseases. As a result, governmental and scientific organizations now recommend increased dietary intake of Omega-3 PUFAs. The availability of ω-3 fatty acids in our diet is obviously crucial for human health [19].

Several experimental studies have shown that taking n-3 PUFA and improving the Omega-6 and Omega-3 ratio could modulate the immune and inflammatory response. After a three-week supplement with EPA 3.2 g and DHA 2.2 g, an increase in EPA content in neutrophils and monocytes was reported. The anti-inflammatory effects of fish oils are partly mediated by inhibition of the 5-lipoxygenase pathway in neutrophils and monocytes, inhibiting the function mediated by leukotriene B4 (LTB4) of leukotriene B5 (LTB5). Furthermore, ω-3 decreases interleukin IL-1 and IL-6 inhibits inflammation. Inflammation is characterized by an increase in prostaglandins, cytokines and other pro-inflammatory mediators. ROS produce peroxidation of phospholipid membranes and damage DNA and intracellular proteins. A diet rich in n-3 PUFA provides photoprotection and counteracts the risk of ultraviolet-induced skin cancers. In addition to modifying the production of eicosanoids, n-3 PUFAs can also reduce the activation of the NF-KB pathway, reducing the production of inflammatory cytokines that contrast with Omega-6 AA fatty acid, which is a well-known stimulator of NF-KB activity [19].

Omega 3 food sources

The primary source of Omega-3 PUFA in the human diet is marine products. Specifically, marine phytoplankton and other single-cell algae are the main producers of Omega-3 PUFAs, in particular EPA and DHA, and represent the base of the food web for all aquatic creatures.

Humans get Omega-3 PUFAs through multiple levels of this food web: microalgae, which are used directly for food or as animal feed; fish, which directly consumes phytoplankton or eats other animals that feed on phytoplankton; and livestock, which are fed with flour produced by various organisms in the food chain. In essence, phytoplankton is the origin of most of our ω-3 PUFAs.

While terrestrial plants such as flax seeds are a good source of another ω-3 PUFA, alpha-linolenic acid (ALA), a very low metabolic conversion (<5%) of ALA in EPA and DHA makes the sources of land insufficient to meet our dietary needs, as these three types of ω-3 PUFAs have distinct biological functions, with more advantageous EPA and DHA. Marine phytoplankton, due to the relatively high fatty acid composition of EPA and DHA, is therefore particularly valuable for maintaining the availability of important Omega-3 fatty acids in our diet. However, phytoplankton is very vulnerable to climate and environmental changes.

Global climate change could significantly affect the overall availability of long-chain Omega-3 PUFAs in two ways: 1) reducing the overall phytoplankton biomass and growth rate, and 2) reducing the algal content of PUFAs, due to a decrease in PUFA synthesis or destruction of PUFA already synthesized [19].

ω-3 fatty acids are also called "vitamin F" from "fatty acids". EPA and DHA are found in fish with cold water, which have a greater amount of body fat, although their EPA and DHA content depends on some variables such as climate, environment and fish diet. The ALA is found in flaxseed, canola oil (rape seed), soybean, pumpkin seeds, perilla seed oil, walnuts and derivative oils. The health effects come mainly from EPA and DHA. ALA from flax and other vegetarian sources must be converted into the body in EPA and DHA. Other important marine sources of PUFA n-3 include krill, algae, microalgae and crustaceans. Krill oil, particularly Antarctic krill, is a rich source of antioxidants, such as marine carotenoids (eg astaxanthin and fucoxanthin), vitamins A and E and phospholipids containing the long chain n-3 PUFA [Table 2]. In fact, alternative EPA and DHA marine sources such as sponges, bacteria, fungi, plants and, in particular, autotrophic macroalgae and microalgae, are currently being explored for large-scale commercial production of Omega-3 because of their optimal balance between fatty acids -3 and n-6. In particular, the brown and red algae are characterized by the presence of EPA and ALA as well as the green algae are rich in hexadecatetraenoic acid and octadecatetraenoic acid, which is abundant in Laminaria sp. and Undaria pinnatifida [19].

III. OMEGA 3 AND SKELETAL MUSCLE

Skeletal muscle is highly adaptable to alterations in substrate availability and can pass from lipid and glucose oxidation in response to changes in environmental conditions. The ability to switch between different fuel sources, called metabolic flexibility, has decreased in the case of obesity, type 2 diabetes, rest and during exercise.

Skeletal muscle performance is generally determined by the use of standard measurements such as the rate of muscle protein synthesis, muscle mass, maximum voluntary contraction, rate of couple development and markers of muscle damage.

There is growing evidence that Omega-3 PUFAs also possess anabolic / anti-catabolic properties in skeletal muscle. The balance of muscle proteins is regulated by changes in the ratio of muscle protein synthesis (MPS): breakdown of muscle proteins (MPB). An increase in MPS or a decrease in MPB will lead to a positive balance and ultimately to hypertrophy. Muscle disuse due to illness or injury is associated with severe skeletal muscle loss. However, in some studies, an action of Omega-3 supplementation was shown to mitigate the loss of skeletal muscle mass. It is known that the increase in the availability of amino acids stimulates an increase in MPS and the integration of Omega-3 can enhance the response to anabolic stimuli.

Researchers have seen a positive effect of n-3 PUFAs on anabolism and muscle catabolism not only in cancer cachexia, but also in healthy volunteers, with a positive impact on muscle maintenance. Both in vivo studies [20] and in vitro [21] show a significant increase in muscle protein synthesis in young and elderly subjects after eight weeks of daily administration of 4 g n- 3 PUFA [22]. Similarly, six months of integration (3.36 g / day) resulted in an increase in muscle mass (+ 3.6%) and strength (+ 4%) in older people [22].

Another study concerning muscle recovery and soreness after performing eccentric biceps exercises showed that seven days of supplementation of 3 g/day n-3 of PUFA decreased muscle damage and post-exercise pain [23].

Positive results in muscle recovery and, subsequently, in training adaptation, have been reported in other similar studies. N-3 PUFAs attenuated loss of muscle strength and gamma movement, blood inflammation markers such as TNF-α and markers of muscle damage, such as myoglobin, creatine kinase and troponin I in slow skeletal muscle. Furthermore, DHA appears to increase lipid oxidation and insulin sensitivity in skeletal muscles and may stimulate glycolytic capacity in myocytes; they can probably improve athletic performance, through a modulation on the permeability of cell membranes and on insulin sensitivity, which makes muscle cells more permeable as regards the necessary nutrients, such as glucose and amino acids [19]

The exact mechanism that acts on the process of muscle-protein synthesis is not entirely clear, but it was found to be partially mediated by the increased activation of the mammalian target of rapamycin (mTOR) -prososomal protein S6 kinase beta-1 (p70s6k) signaling pathway, considered an integral control point for muscle cell growth. This results in an anabolic incitement and induces an increase in the rate of muscle-protein synthesis. They can be recommended as a good supplement for athletic populations to improve some aspects of recovery during training or in competition. Furthermore, the action of chronic n-3 PUFA supplementation was demonstrated in enhancing neuromuscular activity in animal studies. [19].

Muscle health and even energy metabolism are a crucial point in exercise performance. In human myotubes, 24-hour pre-treatment with EPA 100 μM increased suppression caused by acute glucose exposure on fatty acid metabolism and increased flexibility regulated by the energy substrate. All these studies suggest that Omega-3 PUFAs, particularly EPA, play a beneficial role in maintaining the total protein balance.

One of the main causes underlying muscle wasting conditions, such as sarcopenia, is believed to be an altered MPS response to anabolic stimuli. Omega-3 PUFAs may therefore be potentially relevant to the clinical environment as a non-pharmacological method to reduce muscle loss. Further long-term studies in humans are necessary to establish whether long-term Omega-3 supplementation leads to muscle hypertrophy and the consequent functional gains. Furthermore, the question remains whether Omega-3 PUFAs not only improve the MPS response to nutrition, but also increase MPS after an acute exercise of resistance exercise. Tissue culture model experiments indicate that EPA can make a significant contribution to changes in MPS rather than DHA, however, it has yet to be confirmed in humans if EPA underlies changes in muscle mass and function [15].

Some studies suggest that both EPA and DHA may have a protective effect against fatty acid-induced insulin resistance. Although excessive simplification, ω-6 fatty acids, especially arachidonic acid (AA, 20: 4) have a more powerful inflammatory effect than ω-3 PUFAs. While transient inflammation is an important process in muscle adaptation, the inability to effectively resolve the inflammation that leads to a chronic state of inflammation is associated with obesity. There is growing evidence that Omega-3s are potent anti-inflammatory drugs [24]. Synergistically, EPA and DHA play a role in the resolution of inflammation through inflammatory mediators derived from EPA and DHA such as prostaglandins, leukotrienes, lipoxins, resolvins and proteins. The anti-inflammatory effect of EPA and DHA depends mainly on incorporation into phospholipids.

In addition to modifying the production of eicosanoids, ω-3s can also reduce the activation of the NF-KB pathway, reducing the production of inflammatory cytokines by counteracting the ω-6 AA fatty acid which is a known stimulator of NF activity KB [25].

In vivo studies evaluating the immunomodulatory effect of ω-3 PUFAs in humans are limited. However, a diet rich in EPA and DHA is inversely associated with concentrations of c reactive protein [26].

There is emerging evidence that several Omega-3 PUFAs have divergent metabolic functions and further research is needed to understand the different mechanisms underlying these effects. Recent advances in "omics" techniques and in mass spectrometry technology will allow a comprehensive and sensitive approach to the analysis of metabolic changes induced through the absorption of Omega-3. Currently, ω-3s derive mainly from marine sources, but the increasing environmental pressures on fish populations question the sustainability of fish as an adequate resource for this nutraceutical. It is estimated that by 2050 the human population will reach 9.175. This highlights the need to understand the mechanisms of the action of Omega-3 that can lead to the development of an ω-3 camouflage and provide a sustainable long-term source [15].

IV. OMEGA 3 AND PHYSICAL PERFORMANCE

Western diets are high in n-6 and low in n-3, competing for incorporation into the second position of labile phospholipids in cell membranes. n-6 PUFA, mainly linoleic acid, is a precursor of arachidonic acid, which is a substrate of cyclooxygenase and lipoxygenase enzymes that leads to a pro-inflammatory environment that will cause damage in different tissues, including muscles. On the other hand, n-3 PUFAs exert pleiotropic actions on many tissues, in particular on the cardiovascular system and on the central nervous system, which could be protective against age-related diseases. The central nervous system has a high concentration of complex lipids, which determine the structural and functional properties of its cellular and subcellular membranes. Fish oil supplementation, rich in n-3 PUFA, has been shown to increase nerve conduction velocity in the elderly, modulate sarcolemma ion channel and improve cardiac contractile activity. Therefore, since the integration of fish oil improves both the contractility of the heart muscle and the speed of nerve conduction, it is reasonable to hypothesize that it may enhance the strength training effects on skeletal muscles [Table 3]. There is a lack of studies reporting the effects of fish oil supplementation on neuromuscular function in the elderly and the lack of information on the duration of supplementation and dose [27].

There is evidence in humans that Omega-3 PUFAs improve MPS response to nutrition and evidence from in vitro and rodent cancer models that supplementation with Omega-3 PUFA reduces muscle protein breakdown. However, it is not clear whether long-term integration of Omega-3 can improve muscle function [15]

Rodacki et al. [27] were the first to assess whether Omega-3 supplementation could improve muscle function in the elderly when combined with resistance training. They studied the effect of fish oil supplementation and strength training on the neuromuscular system (muscle strength and functional capacity) of a sample of elderly women. 45 women (aged between 64 and 1.4 years) were randomly assigned to 3 groups with a 90-day progressive resistance exercise program. One group performed only strength training (group ST) for 90 days, while the others performed the same strength training program and received fish oil supplementation, namely Omega-3 fatty acids, (2 g/day) for 90 d (group ST90) or for 150 d (group ST150; 60 days before training). Muscle strength and functional capacity were assessed before and after the training period. No difference in the pre-treatment period was found between the groups for any of the variables. The maximum torque and the rate of torque development for all muscles (flexor knee and extensor, plantar and flexor dorsi) are increased from pre-post-training in all groups. However, a greater effect was observed in the ST90 and ST150 groups compared to the ST group. The level of activation and the electromechanical delay of the muscles have changed from pre-post-training only for the ST90 and ST150 groups. Therefore strength training has increased muscle strength in older women and fish oil supplementation has resulted in greater improvements in muscle strength and functional capacity. Muscle strength and neuromuscular function were significantly improved when Omega-3 supplementation was combined with resistance exercise

Long-chain ω-3 fatty acids help reduce the production of proinflammatory eicosanoids (such as interleukin-6) and promote the production of prostaglandins in the 1 series, which have an anti-inflammatory effect. The intense and frequent workouts that high-level athletes undergo determine an increased risk of accidents (in particular those of repeated micro-traumas and of muscular ones) due to a high production of pro-inflammatory molecules, often unbalanced by adequate production of anti-inflammatory molecules.

Integration with long-chain ω-3 can also be very useful in the prevention and treatment of anemia of the athlete, or a decrease in the amount of red blood cells (which carry oxygen in the blood) linked to iron deficiency: checking the status inflammation of the body facilitates the absorption and release of iron from the body's deposits. Omega-3 fatty acids have also proved useful in improving the efficiency of the central nervous system, especially as regards reaction times and mood. There is now growing evidence that ω-3 PUFAs also have intrinsic anabolic/anti-catabolic properties in skeletal muscle. The balance of muscle proteins is regulated by changes in the ratio of muscle protein synthesis (MPS): breakdown of muscle proteins (MPB).

Although excessive simplification, ω-6 fatty acids, especially arachidonic acid (AA, 20:4) have a more powerful inflammatory effect than ω-3 PUFAs. While transient inflammation is an important process in muscle adaptation, the inability to effectively resolve inflammation leading to a chronic inflammation state is associated with development of insulin resistance IR/T2D type 2 diabetes and obesity. There is growing evidence that Omega-3 PUFAs have powerful anti-inflammatory actions. Synergistically, EPA and DHA play a role in the resolution of inflammation through inflammatory mediators derived from EPA and DHA such as prostaglandins, leukotrienes, lipoxins, resolvins and proteins. The anti-inflammatory effect of EPA and DHA depends mainly on incorporation into phospholipids. EPA and DHA differentially alter the inflammatory response through specific lipid production of lipid mediators. Eicosanoids are synthesized from 20 carbon fatty acid chains that were released from phospholipids by phospholipase A2, which means that both AA and EPA are substrates for the production of eicosanoids. [15].

In addition to modifying the production of eicosanoids, Omega-3 PUFAs can also reduce the activation of the NF-KB pathway, reducing the production of inflammatory cytokines by counteracting the Omega-6 AA fatty acid which is a known stimulator of NF activity-KB [25]

To date, no consensus has been reached on what constitutes an effective dose of Omega-3 PUFA, a question probably confused by individual variation and without apparent dose-response relationship. Previous studies have observed individual consumption of Omega-3 PUFA in tissues, therefore the same period of administration and the same dose can lead to different levels of Omega-3 PUFA tissue between subjects, potentially masking any effect of the increase in levels of PUFA Omega-3 fabric. Both the integration period and the duration of follow-up measures need to be taken into account, as these factors will influence the measurement of the results. For example, Mostad and colleagues observed that the short-term response to Omega-3 PUFA was a decrease in fat oxidation, but the opposite effect was observed after nine weeks [28]. The manipulation of the n-3/n-6 ratio is hypothesized to be an important factor in maximizing the effects of Omega-3 PUFAs; the difficulty, however, is the choice of placebo. Studies using a high-Omega-6 corn oil as a control may also have metabolic effects and may not represent a true placebo.

Potential adverse effects of n-3 PUFAs

Unfortunately, not only drugs, but also nutritional supplements or nutraceuticals could have adverse effects. Despite the benefits listed above, there are potential risks associated with excessive use of PUFA n-3. Important potential side effects include impaired platelet function. The presence of EPA and DHA leads to the production of thromboxane A3, which is a less potent platelet activator than thromboxane A2. EPA and DHA supplementation can therefore affect platelet activation due to the different eicosanoids produced, which leads to to an antithrombotic effect that causes harmful effects for wound healing.

Physicians must understand the adverse effects that may occur with the integration of PUFA n-3 and that potential risks should be evaluated along with the potential benefits. Adverse effects are likely to be dose-dependent. In conclusion, it is necessary to understand the necessary dosages and the food concentration to aim for, when the integration of n-3 PUFA is recommended.

V. CONCLUSIONS

Athletes experience regular cycles of physiological stress accompanied by transient inflammation, oxidative stress and immune perturbations. Exercise activates multiple molecular and biochemical pathways with many involving the immune system, and more and more information indicates that they are sensitive to nutritional influences. Nutritional support has the potential to partially mitigate these exercise-induced changes without interfering with the signaling activities necessary for training adaptations. The most effective nutritional countermeasures for athletes include n-3-PUFA, bovine colostrum, supplements and antioxidants, such as vitamins, carotenoids, polyphenols [19], probiotics, β-glucans and nutraceuticals in general [29]. NFA-3 PUFAs seem to be among the most useful supplements for a wide segment of the population (premature babies, elderly with sarcopenia, athletes and patients with metabolic and inflammatory diseases). Since only Eskimos, Japanese and a few other small groups of people do not require these supplements, these fats should be added to foods, rather than being used exclusively as food supplements. Furthermore, omega-3 retain their properties when packaged in healthy foods other than fish. At the same time, a reduction in the intake of ω-6 is necessary, in order to reduce the ω-6/ω-3 ratio to the extent provided by the evolution of human biology. There is good evidence from studies on the human body and the Paleolithic diet, the Crete diet and the Okinawan diet that the physiological ratio n-6: n-3 should be: 1 or 2:1. Japan has already recommended a 2:1 ratio. Nutritional strategies and supplements such as omega-3 can lead to optimal training gains, enhanced recovery, reduced risk of illness and high-level competitive performance. Furthermore, it was shown that they could influence moods and emotional states. Additional 24 female elite soccer players with 3.5 g per day of DHA-rich fish oil for four weeks produced perceptive-motor benefits (ie, improvements in complex reaction time and efficiency). This supports the idea that DHA can improve performance in sports where perceptive motor activity and decision making are the keys to success [30]. If the observed positive associations are causal, increasing the intake of omega-3 by eating more fish or taking supplements, is an intervention that could be applied to this segment of the population. This could be an ergogenic aid that improves training and sports performance at low cost and with little risk.

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TABLE 1. Some *nutraceuticals* present in food [31].

Nutraceutical	**Chemical constituent**	**Food**
Allicin	Diallyl disulfide	Garlic (allium sativum), onion
Genistein, daidzein	Phytoestrogens	Soy beans, legumes
Lycopene	Caroteinoid	Tomatoes, pink grapefruit, guava papaya, watermelon
Resveratrol	Polyphenolic compound	Dark grapes, raisins, peanuts, berries
β-Carotene	Carotenoid	Carrots, oranges, tangerines, corn, avocado, various fruits and vegetables,
Selenium	Mineral	Sardines, cod, sole, walnuts, peas
Catechin, epicathechin	Polyphenolic compounds	Tea (extracted from *Camellia sinensis*), citrus, apples, berries
Qurcetin	Polyphenols	
Omega 3 Fatty acids (PUFA, Polyunsaturated fatty acids)	Fatty acids	Salmon, flax seed
Lactobacilli, bifidobacteria	Probiotics/prebiotics	Yogurt, dairy applications
Retinol	Vitamin A	Beef liver, hen eggs, dairy products
Curcumin	Polyphenolic compound	Turmeric root
Folic acid	Vitamin B	Hen eggs, goat liver, cereals, pulses and green leafy vegetables

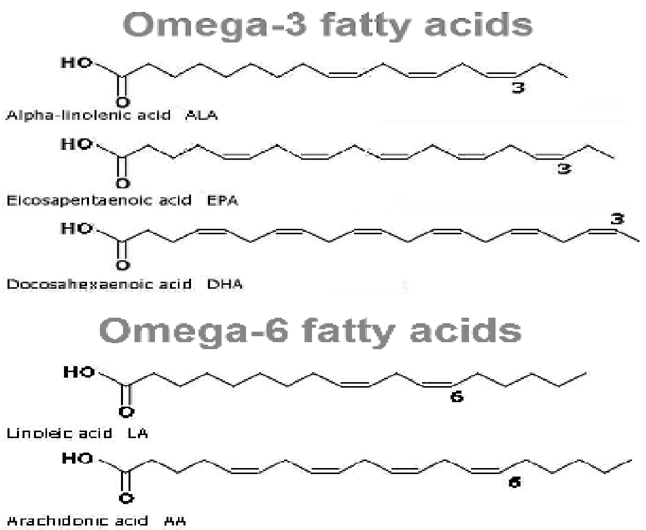

Figure 1. Essential fatty acids.

TABLE 2. Foods source of omega-3 fats. ALA is found in certain vegetable oils, walnuts, flaxseeds and soy products. EPA and DHA are found in fish, seafood and fish oils.

Omega 3 rich foods (g/100g)	ALA	EPA	DHA	Omega 3
Walnuts	6.64	-	-	6.64
Mackerel	0.15	0.73	1.26	2.14
Salmon	0.09	0.89	1.19	2.17
Tuna	0.09	0.89	2.15	3.04
Anchovies	0.01	0.27	0.52	0.8
Flaxseeds	17.1	-	-	17.1
Soybean oil	7.6	-	-	7.6
Cod	0	0.03	0.08	0.11
Mussels	0.04	0.27	0.11	0.42
Chicken thigh	0.03	0.03	0.11	0.17
Drained canned tuna	0.01	0.05	0.22	0.28
Cow milk	0.05	-	-	0.05

TABLE 3. Summary of the effects in humans of ω3-PUFA supplementation on muscle damage and inflammatory response to exercise, and physical performance [30].

14 Trained Males	2,224 mg EPA, 2,208 mg DHA per Day for 6 Weeks	Significantly Reduced Resting Levels of Inflammatory Biomarkers, No Significant Effect on Exercise-Induced Inflammation or Oxidative Stress
27 Healthy Untrained Males	324 mg EPA, 216 mg DHA per day for 30 days	No Change in Pain Level, Knee ROM Before, Immediately, and 24 Hours Postexercise; Significant Decrease in Perceived Pain, Thigh Circumference, and ROM 48 Hours Postexercise
20 Endurance-Trained Males	3.6 g per Day Fish Oil (51% EPA and 31% DHA) per Day for 6 Weeks	Significantly Reduced Acute-Phase Response and Cytokine Release Associated With Exercise
20 Elite Male Swimmers	1.8 g Fish Oil per Day, With 950 mg EPA, 500 mg DHA, for 6 Weeks	Significantly Reduced Plasma Levels of AA, PGE_2, IFN-γ, and TNF-α; Significantly Increased IL-2
36 Trained Males	2 g Fish Oil per Day, With 600 mg EPA, 400 mg DHA, for 6 Weeks	Significantly Increased Oxidative Stress at Baseline, Did Not Attenuate Increased Oxidative Stress Resulting From Exercise
24 Male Trained Cyclists	6 g Fish Oil per Day for 3 Weeks	No Change in 1-Hour Time Trial Performance
28 Male Soccer Players	5.2 g Fish Oil per Day, With 1.6 g and 1.04 g DHA, for 10 Weeks	No Change in Aerobic Power or Running Performance
25 Male Football	6 g Fish Oil per Day, With 0.36	No Change in Endurance Exercise No Change in Endurance Exercise
11 Male Cyclists	2,000 mg EPA, 400 mg DHA per Day, for 6 Weeks	Fish Oil Supplementation Associated With Increase in F2-Isoprostanes in Response to Heavy Cycling Exercise; Supplementation With Antioxidant Vitamins and Minerals Attenuates the Increase in F2-Isoprostanes; No Increase in FRAP
23 Trained Cyclists	2.4 g Fish Oil per Day, With 3 g EPA and 0.4 g DHA, for 6 Weeks	No Change in 10-km Time Trial Performance
16 Male Cyclists	8 g Fish Oil Per Day for 8 Weeks	Heart Rate, VO2, Rate Pressure Product Lower During Steady State Endurance Exercise, but No Change in Performance

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