Omega-3 Polyunsaturated Fatty Acids in Physical Performance Optimization

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Increased muscle oxidative stress and inflammatory responses among athletes have been reported consistently. In addition, it is well known that exhaustive or unaccustomed exercise can lead to muscle fatigue, delayed-onset muscle soreness, and a decrement in performance. Omega-3 polyunsaturated fatty acids (PUFAs) have been shown to decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species; have immunomodulatory effects; and attenuate inflammatory diseases. While a number of studies have assessed the efficacy of omega-3 PUFA supplementation on red blood cell deformability, muscle damage, inflammation, and metabolism during exercise, only a few have evaluated the impact of omega-3 PUFA supplementation on exercise performance. It has been suggested that the ingestion of EPA and DHA of approximately 1–2 g/d, at a ratio of EPA to DHA of 2:1, may be beneficial in counteracting exercise-induced inflammation and for the overall athlete health. However, the human data are inconclusive as to whether omega-3 PUFA supplementation at this dosage is effective in attenuating the inflammatory and immunomodulatory response to exercise and improving exercise performance. Thus, attempts should be made to establish an optimal omega-3 fatty-acid dosage to maximize the risk-to-reward ratio of supplementation. It should be noted that high omega-3 PUFA consumption may lead to immunosuppression and prolong bleeding time. Future studies investigating the efficacy of omega-3 PUFA supplementation in exercise-trained individuals should consider using an exercise protocol of sufficient duration and intensity to produce a more robust oxidative and inflammatory response.

Keywords: fish oil, exercise, inflammation, PUFAs

Over the past 3 decades, there has been substantial interest in the therapeutic potential of fish oils for various inflammatory conditions such as rheumatoid arthritis, inflammatory bowel diseases, and asthma in humans. In addition, fish oil, rich in omega-3 polyunsaturated fatty acids (PUFAs), exerts anti-inflammatory and immunomodulatory effects and may be useful as a nutritional countermeasure to exercise-induced inflammation and immune dysfunction in athletes. The omega-3 PUFAs such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish oil appear to have additional anti-inflammatory properties, primarily through their effects on the neutrophil and macrophage components of the inflammatory response (Lee et al., 1985).

Initial interest in the cardiovascular benefits of EPA and DHA was provoked by the finding that the Greenland Eskimos and other populations who consume diets rich in these fatty acids have remarkably low incidences of cardiovascular diseases (Dyerberg, Bang, & Hjorne, 1975; Yamori, Nara, Iritani, Workman, & Inagami, 1985). A large number of both experimental and epidemiological studies have since been conducted to examine the effect of consuming fish oil, which contains high amounts of EPA and DHA, on cardiovascular health, with most showing an inverse correlation on morbidity and mortality (Albert et al., 2002; Hu et al., 2002; Lemaitre et al., 2003; Oomen et al., 2000; Rissanen, Voutilainen, Nyyssonen, Lakka, & Salonen, 2000; von Schacky, Angerer, Kohthy, Theisen, & Mudra, 1999). The cardioprotective effects of omega-3 fatty acids are ascribed to improvements in various cardiovascular risk factors including a reduction in blood-platelet aggregation (Mori, Beilin, Burke, Morris, & Ritchie, 1997; Phang, Sinclair, Linez, & Garg, 2012), decreased inflammation (Heller, Koch, Schmeck, & van Ackern, 1998; Zhao et al., 2004), enhanced endothelial function (Fleischhauer, Yan & Fischell, 1993), positive changes in blood lipids (Calabresi et al., 2004; Harris, 1989; Herrmann, Biermann, & Kostner, 1995), and decreased blood pressure (Paschos, Magkos, Panagiotakis, Votteas, & Zampelas, 2007; Prasad, 2009).

EPA and DHA, derived from fish oil, can cause dual inhibition of cyclo-oxygenase-2 and 5-lipoxygenase pathways for metabolism of arachidonic acid (AA). EPA is a much less preferred substrate than AA for both pathways and generally by substrate competition inhibits release of AA-derived eicosanoids, thus reducing the generation of proinflammatory “tetraene” 4-series leukotrienes and 2-series prostanoids and production of cytokines from inflammatory cells (Mickleborough,
2008). Consuming fish oil results in partial replacement of AA in inflammatory-cell membranes by EPA and thus demonstrates a potentially beneficial anti-inflammatory effect of omega-3 PUFAs. Supplementing the diet with omega-3 PUFAs has been shown to reduce AA concentrations in neutrophils, reduce neutrophil chemotaxis, and reduce leukotriene generation (Lee et al., 1985). The effects of omega-3 PUFAs on inflammatory cytokine gene expression suggest that they modify the activity of the transcription factors nuclear factor κB and/or peroxisome proliferator-activated receptor (PPAR)-γ (Calder, 2009).

Long-chain omega-3 PUFAs have not only been shown to decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species but also have shown to possess immunomodulatory effects (Calder, 2007). It appears that the EPA and DHA membrane composition of immune cells can be altered with long-term ingestion of omega-3 PUFAs, which can influence phagocytosis, T-cell signaling, and antigen-presenting capabilities (Calder, 2007).

This review focuses on both human and animal studies that assessed the effectiveness of omega-3 PUFA supplementation on the physiological response to exercise. Few human studies, of which the results are equivocal, have been conducted to assess the efficacy of omega-3 PUFAs on inflammatory, immunomodulatory, and subsequent exercise response in healthy individuals. However, studies evaluating the impact of omega-3 PUFA supplementation on exercise metabolism, muscle damage, and endurance-exercise performance in animals have yielded promising results. In addition, given the purported benefits of omega-3 PUFAs on the cardiovascular system and carbohydrate fat and protein metabolism, it has been hypothesized that supplementation with these fatty acids may enhance the beneficial effects of physical activity, potentiating enhanced lipid oxidation and improvements in exercise performance.

For this review, the keywords eicosapentaenoic acid, docosahexaenoic acid, omega-3 PUFA, omega-6 PUFA, and fish oil were coupled with keywords exercise performance, physical performance, red blood cell deformability, protein metabolism, inflammation, muscle damage, exercise metabolism, exercise cardiac function, blood flow, lipids, and migratory flight performance for a MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Google Scholar, and SPORTDiscus search.

Discussion

Omega-3 Fatty Acids and Red Blood Cell Deformability

Red blood cell (RBC) deformability decreases with exercise (Galea & Davidson, 1985; van der Brug, Peters, Hardeman, Schep, & Mosterd, 1995) and is associated with increased aggregation and transit time through micropores (Simchon, Jan, & Chien, 1987; Yalcin, Bor-Kueukatay, Senturk, & Baskurt, 2000), which may reduce the efficacy of oxygen delivery through the microcirculation. RBC deformability refers to the cellular properties of RBCs, which determine the degree of shape change under a given level of applied force. RBCs can significantly change their shape while passing through the microcirculation. RBC deformability is a measurable property, and the preferred method for measuring deformability is to use the ektacytometric principle, which is based on laser-diffraction analysis (Baskurt et al., 2009). Briefly, RBCs are exposed to increasing shear stress, and the laser diffraction pattern through the suspension is recorded; it goes from circular to elliptical as shear increases. From these measurements, a deformability index for the cells can be derived (Baskurt et al., 2009; Oostenbrug et al., 1997).

A number of studies have shown that dietary fish oil increases the deformability of RBCs as a consequence of incorporation of omega-3 PUFAs into RBC membrane phospholipids (Andersson, Nalsen, Tengblad, & Vessby, 2002; Cartwright, Pockley, Galloway, Greaves, & Preston, 1985; Terano et al., 1983). Omega-3 PUFAs have also been shown to facilitate the transport of RBCs through the capillary bed (Bruckner, Webb, Greenwell, Chow, & Richardson, 1987), which could lead to enhanced oxygen delivery to skeletal muscle and a subsequent improvement in exercise performance. In clinical studies, fish-oil supplementation (2.8 g EPA/day for 3 months) enhanced RBC deformability in patients with angina (Solomon et al., 1990) and increased RBC deformability after supplementation of 1.8 g EPA and 1.2 g DHA/day for 4 months in patients with claudication.

Several studies have investigated the effects of fish-oil supplementation on RBC deformability and subsequent exercise performance. Guezennec, Nadaud, Satabin, Leger, and Lafargue (1989) evaluated the effect of 6 g (1,080 mg EPA and 720 mg DHA) of fish-oil supplementation given daily over 6 weeks on RBC deformability after hypobaric exercise. Although the omega-3 PUFA was incorporated into the RBC membranes, this inclusion did not result in a significant change in RBC deformability at rest. The RBC phospholipid content of EPA (20:5) and DHA (22:6), expressed as a weight percentage of total fatty-acid content, was significantly increased after fish-oil supplementation (EPA, 3.9% ± 0.30%; DHA, 6.40% ± 0.28%) compared with the control group (EPA, 1.8% ± 0.22%; DHA, 4.28% ± 0.15%). However, after hypobaric exercise, RBC deformability decreased less on than he fish-oil diet compared with the normal diet. Guezennec et al. concluded that VO2max increased and oxygen saturation decreased after 6 weeks of fish-oil supplementation. However, the data from that study are difficult to interpret since the same power output, with an increased VO2max, was observed. Oostenbrug et al. (1997) investigated the effects of 3 weeks of fish-oil supplementation (6 g/day) and vitamin E (300 IU/day) on RBC deformability and lipid peroxidation in 24 trained cyclists. Exercise performance (1-hr time trial) and RBC characteristics were not improved by fish oil. Malaguti, Baldini, Angeloni, Biagi, and Hrelia...
(2008) evaluated the role of a high-protein, low-calorie, PUFA-enriched (3 g/day) diet and a Mediterranean diet on anthropometrics, RBC fatty-acid composition, and plasma antioxidant defenses among nonprofessional volleyball athletes. They found that total antioxidant activity increased in both groups and that RBC-membrane PUFA content increased and body-mass index and total body fat (calculated using skinfold-based body-fat estimation) were significantly reduced only in the fish-oil-supplemented group. There is some concern that incorporating omega-3 PUFAs into cell membranes may increase the potential for lipid peroxidation (Pedersen et al., 2003), which is much more evident in athletes who undergo high oxidative stress (Allard, Kurian, Aghdassi, Muggli, & Royall, 1997). While it is clear that pharmaceutical-grade fish oil leads to an increase in RBC-membrane PUFA content and hence an improved hemorrheological response in athletes, it is unclear if the positive effects of fish-oil supplementation could unfavorably affect these benefits. It is possible that the balance between beneficial and harmful effects of PUFAs depends on dose.

EPA has been shown to be incorporated more efficiently than DHA into RBC membranes (Gans et al., 1990). An increased amount of PUFAs has been found in the phospholipid membranes of RBCs in trained versus untrained skeletal muscle (Andersson, Sjodin, Hedman, Olsson, & Vessby, 2000; Helge et al., 2001). In Helge et al.’s study (2001), 7 male subjects performed endurance training of the knee extensors of one leg for 4 weeks. The other leg served as a control. Before, after 4 days, and after 4 weeks, muscle biopsies were obtained from the vastus lateralis. After 4 weeks, the phospholipid fatty-acid contents of oleic acid 18:1(n-9) and DHA 22:6(n-3) were significantly higher in the trained (10.9% ± 0.5% and 3.2% ± 0.4% of total fatty acids, respectively) than the untrained leg (8.8% ± 0.5% and 2.6% ± 0.4%). This discrepancy was not explained by different fiber-type distribution alone but possibly that differences in the eccentric-exercise protocol or the muscle groups that were studied contributed to the differences in findings between the two studies (Lenn et al., 2002; Tartibian et al., 2009).

Omega-3 Fatty Acids, Muscle Damage, and Inflammatory Response to Exercise

Consistent findings of elevated oxidative stress and inflammatory responses in exercise-trained individuals have been observed in athletes who engage in long-duration exercise such as marathon or triathlon competitions (Fisher-Wellman & Bloomer, 2009). Chronic strenuous exercise itself has been demonstrated to promote impaired immune function (Brenner, Shek, & Shephard, 1994). Intense exercise training leads to muscle fatigue, soreness, dehydration, muscle structural damage, free-radical damage, lactic-acid build-up, neutrophilia, muscle swelling, central-nervous-tissue fatigue, and catabolism of nutrient stores (Armstrong, Warren, & Warren, 1991).

Inflammation is a physiological response to injury or tissue damage that involves the immune system to mediate local defenses. The inflammatory response is characterized by increased expression of cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-1β, and IL-6 (Northoff & Berg, 1991). Cytokines can trigger the release of acute-phase proteins and inflammatory mediators such as leukotrienes and prostaglandins. Increases in oxidative stress after a bout of strenuous exercise (Sen, 1995) are accompanied by a diminution in natural immunity and decreased resistance to infection. It has been shown that supplementation with 1.75 g/day EPA and 1.05 g/day DHA for 3 weeks attenuates the rise in acute-phase proteins occurring after exercise (Ernst, Saradeth, & Achhammer, 1991) and stops postexercise immunosuppression of the immunoglobulin M-plaque-forming response (Benquet et al., 1994). Tartibian, Maleki, and Abbasi (2009) assessed the effect of 324 mg/day EPA and 216 mg/day DHA administered over 30 days before and during 48 hr after step training. The control group (n = 9) received no supplement, while the placebo group (n = 9) received a matching placebo capsule. The omega-3 PUFA group (n = 9) also received 100 IU of d-α-tocopherol/dl-α-tocopherol acetate to minimize long-chain unsaturated fatty-acid oxidation (Sen et al., 1997). While no significant difference was observed between groups for pain level of the lower limbs and knee range of motion before, immediately after, and 24 hr after the exercise, a significant decrease in indirect indices of delayed-onset muscle soreness (DOMS), such as perceived pain, thigh circumference (indicator of muscle swelling/inflammation), and range of motion, and were seen 48 hr after exercise in the omega-3 PUFA group compared with the placebo and control groups. In contrast, Lenn et al. (2002) examined the effects of 1.8 g/day of fish oil and isoflavones on DOMS for 30 days before and after 7 days of eccentric exercise and found no significant effects of attenuated perceived pain. It is possible that differences in the eccentric-exercise protocol or the muscle groups that were studied contributed to the differences in findings between the two studies (Lenn et al., 2002; Tartibian et al., 2009).

Recently, Bloomer, Larson, Fisher-Wellman, Galpin, and Schilling (2009) examined the efficacy of EPA (2,224 mg/day) and DHA (2,208 mg/day) for 6 weeks on resting and exercise-induced inflammation, oxidative stress, and aerobic exercise (60-min walk on a treadmill while carrying a weighted backpack equal to 25% of body mass). The treadmill speed and grade were altered every 5 min to mimic the type and duration of exercise performed by the military in a typical physical march. Bloomer et al. found that the EPA/DHA supplementation significantly increased plasma levels of these fatty acids and significantly reduced resting levels of inflammatory biomarkers (i.e., C-reactive protein and TNF-α) but did not have any significant effect on exercise-induced inflammation or oxidative stress (i.e., total antioxidant capacity, protein carbonyls, malondialdehyde, hydrogen peroxide, xanthine oxidase, and nitric oxide). They concluded that the latter finding may be due to the fact that trained men exhibit minimal inflammation.
and oxidative-stress responses to moderate aerobic exercise. There are a number of possible explanations as to why Bloomer et al. did not observe an attenuation of exercise-induced inflammation and oxidative stress on the EPA/DHA-rich diet. It is possible that the exercise protocol they chose was too low in intensity and duration to promote significant oxidative stress and inflammation in their sample of trained men. In addition, they chose a protocol that was concentric in nature, and therefore the amount of muscle damage (and subsequent related reactive oxygen and nitrogen species) would be expected to be minimal. This was confirmed by their finding of insignificant increases in muscle soreness and creatine kinase levels in the blood. Thus, their results may have been different if they had used either an aerobic-exercise bout involving an eccentric component (e.g., downhill running) or a heavy-resistance-exercise protocol. Jouris, McDaniel, and Weiss (2011) recently demonstrated that 2,000 mg EPA and 1,000 mg EPA taken daily over 7 days reduced exercise-induced muscle soreness (i.e., using a visual analog scale when “weighted”—while the participantsflexed and extended their elbow while holding a 1.1-kg weight—and when “fully extended”—participants attempted to fully extend their elbow) induced by eccentric arm-curl exercise compared with baseline and a control group (no supplement).

Toft et al. (2000) investigated whether 3.6 g/day of fish-oil supplementation (53% EPA and 31% DHA) and 21.6 mg tocopherol taken for 6 weeks was able to reduce the acute-phase response and increased cytokine release associated with strenuous exercise in 20 endurance-trained men. While they found that strenuous exercise (marathon running) did increase plasma levels of TNF-α, IL-6, IL-1α, and transforming growth factor-β1, fish-oil supplementation did not affect the exercise-induced cytokine increase, despite incorporation of omega-3 PUFA into blood mononuclear cell plasma membranes. In contrast, Andrade, Ribeiro, Bozza, Costa Rosa, and Tavares do Carmo (2007) found that 6 weeks of 1.8-g/day fish-oil supplementation (950 mg EPA and 500 mg DHA) given to elite swimmers during a period of intense training significantly increased plasma levels of EPA and DHA and significantly reduced plasma levels of AA compared with their placebo group. In addition, the fish-oil-supplemented group exhibited significant reductions in prostaglandin E2, interferon-γ, and TNF-α and a significant increase in IL-2. It is important to note that both IL-2 and interferon-γ are important in the establishment of balance of the TH1/TH2 response, and thus Andrade et al.’s findings are important since the data indicate that fish-oil supplementation can influence immune responses in elite swimmers during periods of intense training. Whether these findings translate into improved exercise performance has yet to be studied.

Poprzecki, Zajac, Chalimoniuk, Waskiewicz, and Langfort (2009) recently sought to elucidate whether a low dose of omega-3 PUFA and exercise could enhance blood antioxidant status and influence blood plasma lipid profile. They found that 6 weeks of a low dose of n-3 PUFA (1.3 g/day; 30% EPA, 20% DHA, and 4 mg α-tocopherol) in untrained healthy subjects partially protected against the reduced superoxide dismutase in response to acute endurance exercise (1 hr of cycling exercise at 60% VO2max) and increased catalase activity during recovery periods compared with placebo. Furthermore, they found that omega-3 PUFA supplementation did not significantly alter oxygen consumption during exercise or the blood plasma lipid profile compared with placebo. They concluded that the beneficial effect of omega-3 PUFA supplementation during endurance exercise may be attributable to the activation of the superoxide dismutase and catalase pathways. On the other hand, Filaire et al. (2011) recently showed that 6 weeks of daily supplementation with 600 mg EPA and 400 mg DHA increased oxidative stress at baseline in trained men and did not attenuate the increased oxidative stress resulting from exercise (cycling exercise to exhaustion). Addition of antioxidants (30 mg vitamin E, 60 mg vitamin C, and 6 mg β-carotene) to the diet did not prevent the formation of oxidation products at rest. On the contrary, the combination of antioxidants added to the omega-3 PUFA supplement led to a decrease in malondialdehyde and lipoperoxide concentrations, maximal rate of oxidation during the propagating chain reaction, and the maximum amount of conjugated dienes accumulated after the propagation phase following a judo training session.

Given the antagonistic effects of n-3 PUFAs on pro-inflammatory eicosanoids (Calder, 2006), supplementation may help alleviate DOMS, which could indirectly benefit exercise performance. In addition, positive effects on DOMS may be augmented by the ability of n-3 PUFAs to increase blood flow (Stebbins, Hammel, Marshal, Spangenberg, & Musch, 2010; Walser, Giordano, & Stebblins, 2006), thereby aiding in a more rapid nutrient delivery postexercise. However, further studies are needed to determine whether n-3 PUFAs may, in fact, produce analgesic effects.

**Omega-3 Fatty Acids and Exercise Metabolism**

During high-intensity exercise, hepatic glucose production (HGP) and glucose utilization are stimulated to prevent hypoglycemia (Trimmer et al., 2002). Endurance training leads to increased fat and decreased carbohydrate oxidation, which is concomitant with a reduction in HGP (Coggan, Kohrt, Spina, Bier, & Holloszy, 1990). Puhakainen, Ahola, and Yki-Jarvinen (1995) observed enhanced gluconeogenesis without increased HGP in 9 obese patients with Type II diabetes who consumed fish-oil supplements (12 g/day). Delarue, Labarthe, and Cohen (2003) examined the effect of 3 weeks of fish-oil supplementation (6 g/day) and exercise on plasma glucose disappearance and HGP in 6 untrained males. At rest, HGP and plasma glucose disappearance were unchanged in the fish-oil-supplementation group compared with the control group. However, during the two 90-min cycling bouts (60% of VO2max) the fish-oil-supplemented group...
demonstrated a reduced plasma glucose-disappearance rate and a reduced HGP, by 26% and 21%, respectively, and reduced glucose metabolic clearance rate compared with the exercise controls. In addition, after exercise, lipid oxidation was enhanced and carbohydrate oxidation decreased after fish-oil supplementation, supporting the assumption that fish oil may reduce the glucose metabolic clearance rate by facilitating fat oxidation.

Endurance training and/or a fish-oil-supplemented diet can affect cytoplasmic fatty-acid-binding protein (FABP[c]) content in rat skeletal muscles and heart (Clavel, Farout, Briand, Briand, & Jouanel, 2002). After 8 weeks of swimming, 34 trained rats exhibited higher FABP(c) content in the extensor digitorum longus and in the gastrocnemius than did the 32 control rats. The FABP(c) increase was associated with an increase of citrate synthase activity (85% and 93%, respectively, in the two muscles), whereas lactate dehydrogenase activity decreased significantly. Therefore, increasing oxidative capacities of muscle by exercise resulted in a concomitant increase of the FABP(c) content. Giving an omega-3 PUFA-supplemented diet for 8 weeks induced a large rise of the FABP(c) in extensor digitorum longus (300%), gastrocnemius (250%), soleus (50%), and heart (15%) without a concurrent accumulation of intramuscular triglycerides or modification of citrate synthase activity. These results suggest that omega-3 PUFAs may increase FABP(c) content by up-regulating fatty-acid metabolism genes via PPAR-α activation. Endurance-trained rats fed with the omega-3 PUFA-rich diet had similar FABP(c) content in the gastrocnemius muscle compared with sedentary omega-3 PUFA-fed rats, whereas an additive effect of exercise and diet was observed in the extensor digitorum longus. As a result, both exercise and the omega-3 PUFA-enriched diet influenced FABP(c) content in muscle. These two physiological treatments presumably acted on FABP(c) content by increasing fatty-acid flux within the cell (Clavel et al., 2002). The shift toward a greater use of fat reduces the rate of glycogen depletion and thus fatigue.

Since both n-3 and n-9 PUFA may increase fat oxidation, Boss, Lecoultre, Ruffieux, Tappy, and Schneider (2010) recently evaluated the combined effects of endurance training and these unsaturated fatty acids on physical performance, fat oxidation, and insulin sensitivity in 16 sedentary male subjects. Subjects were randomly assigned to either an isoenergetic diet with fish oils and olive oils (52% unsaturated fatty acids [UFA], 12% SFA, 6% monounsaturated fatty acids [MUFA], 5% PUFA, 14% protein) or a control diet and underwent a 10-day gradual endurance-training program. While training significantly increased time to exhaustion during cycling exercise at 80% VO2max and improved insulin sensitivity, these effects were not different between groups (UFA and control). In addition, there was no difference in VO2max or fat oxidation between groups. Boss et al. concluded that a diet enriched with fish and olive oil does not enhance the effects of a short-term endurance-training protocol in healthy young subjects. A major weakness in that study is that the effects of the UFA on lipid oxidation may have passed undetected due to the small sample size and thus low statistical power. In addition, both groups differed in the amount of PUFA (EPA and DHA) and MUFA (oleate), making it impossible to assign specific effects to either type of fat.

Omega-3 PUFAs are professed to act as metabolic fuel partitioners (Clarke, 2001), up-regulating lipid oxidative enzymes and down-regulating lipogenic gene expression (Jump, Clarke, Thelen, & Liimatta, 1994). This is partly due to the ability of n-3 PUFAs to bind and activate various isoforms of the PPAR (Lin, Ruuska, Shaw, Dong, & Noy, 1999). Although the mechanism by which omega-3 PUFAs activate PPAR-α remain elusive, the oxidized linoleate and arachidonate metabolites 13-hydroxy-9Z,11E-octadecadienoic acid, 15-hydroxy-5Z,8Z,11Z,13E-eicosatetraenoic acid, prostaglandin J2, and 15-deoxy-d′12,14-prostaglandin J2 are generally believed to be natural PPAR ligands (Bell-Parikh et al., 2003; Ide, Egan, Bell-Parikh, & FitzGerald, 2003). Thus, it is likely that oxidative derivatives of omega-3 PUFAs, and their eicosanoid products, bind PPARs (Mishra, Chaudhary, & Sethi, 2004). Hostetler, Petrescu, Kier, and Schroeder (2005) demonstrated that omega-3 PUFAs, as well as their coenzyme A derivatives, but not saturated fatty acids, can directly bind to PPARs. Specifically, the PPAR-α isoform has been shown to play an important role in managing glucose and fatty-acid homeostasis (Su & Jones, 1993), including the expression of numerous gene-encoding proteins involved in lipid transport and oxidation, including hepatic carnitine acyltransferase and hepatic and skeletal-muscle peroxisomal acyl-CoA oxidase (Clarke & Jump, 1997). Putatively, increased PPAR-α should allow a greater reliance on fat for fuel during exercise, while sparing muscle glycogen and improving both body composition and exercise performance.

Several studies have shown that n-3 PUFA supplementation results in greater accretion of muscle proteins in both humans (Neschen et al., 2007; Robinson & Stone, 2006; Schoeller, 1995) and animals (Bergeron, Julien, Davis, Myre, & Thivierge, 2007; Gingrich et al., 2007). In addition, n-3 PUFAs may enhance mTOR/p70S6K signaling (Schoeller, 1995), a pathway thought to be involved in decreasing proteolysis by down-regulating the ubiquitin-proteasome pathway (Warner, Ullrich, Albrink, & Yeater, 1989), which in conjunction with elevated protein synthesis would result in an even greater accretion of muscle proteins. However, it should be noted that none of these studies were performed in conjunction with exercise. Therefore, further research is required to examine whether n-3 PUFA supplementation may potentiate gains in lean muscle mass when combined with exercise.

**Omega-3 Fatty Acids and Human Physical Performance**

A limited number of human studies have been performed directly examining the influence of omega-3 PUFA
supplementation on exercise performance in healthy subjects. Brilla and Landerholm (1990) examined the effects of fish-oil feeding and exercise training in 32 sedentary males. The subjects were supplemented with omega-3 PUFA (4 g/day) and exercised three times per week for 10 weeks. Both the omega-3 PUFA-supplemented exercised and nonexercised groups exhibited an increased aerobic ventilatory threshold compared with controls. Whereas exercise training resulted in an increased VO_{2max}, fish-oil supplementation had no effect on VO_{2max}. Similarly, in a study (Raastad, Hostmark, & Stromme, 1997) performed in well-trained soccer players, omega-3 PUFA (1.6 g/day EPA and 1.04 g/day DHA) had no effect on aerobic power or running performance when they followed their normal training regimen. However, the athletes displayed significantly lower triacylglycerol levels after supplementation. It has been hypothesized that this attenuation in plasma triacylglycerol levels is caused by decreased lipoprotein triacylglycerol secretion and inhibited triacylglycerol synthesis. Huffman, Altena, Mawhinney, and Thomas (2004) reported a trend for improvement in exercise time to volitional fatigue (after jogging for 75 min at 60% VO_{2max}) after 4 g/day (300 mg EPA and 200 mg DHA) of fish oil administered over 4 weeks.

Buckley, Burgess, Murphy, and Howe (2009) recently examined the effects of 5 weeks of omega-3 PUFA (0.36 g/day EPA and 1.56 g/day DHA) supplementation on endurance performance, recovery, and cardiovascular risk factors in elite Australian Rules football players. The data indicated that on the omega-3 PUFA-supplemented diet RBC’s omega-3 PUFA content doubled from baseline and serum triglycerides and heart rate during submaximal exercise were reduced, but no improvement in endurance-exercise performance or recovery was observed. The authors concluded that omega-3 PUFA supplementation improved cardiovascular efficiency during submaximal exercise, which may assist with the sustained performance of submaximal exercise. Walser and Stebbins (2008) showed that 3 g/day EPA and 2 g/day DHA taken over 6 weeks enhanced stroke volume and cardiac output responses to moderate-intensity exercise and tended to augment systemic vascular resistance (in 9 of 12 healthy subjects). They speculated that these effects may be due to attenuation of sympathetically induced vasoconstriction and/or augmentation of vasodilatation in skeletal muscle during exercise, and thus the findings have implications for enhancing oxygen delivery during exercise and improving functional capacity.

Recently, Nieman, Henson, McAnulty, Jin, and Maxwell (2009) investigated the efficacy of 2.4 g (2 g/day EPA and 0.4 g/day DHA) of fish-oil supplementation over 6 weeks on exercise performance, inflammation, and immune measures in 23 trained cyclists before and after a 3-day period of intense exercise. While a significant increase in plasma EPA and DHA was observed, no changes after 6 weeks of fish-oil supplementation were seen in inflammatory measures (IL-1ra, IL-6, and IL-8), immune measures (blood leukocytes, C-reactive protein, creatine kinase, salivary-IgA, and myeloperoxidase), or 10-km time-trial performance (~65% of maximum power output). Nieman et al. employed a more robust research design than many of the studies examining the influence of fish-oil supplementation on inflammatory and immune measures and exercise performance. However, there are a few possible explanations for the negative outcomes of their study. First, it is highly unlikely that the 3 days of intensified training (cycling) induced a sufficiently high oxidative and inflammatory stress, and, second, the dosage of fish oil used is low compared with other studies (Huffman et al., 2004; Mickleborough, Lindley, Ionescu, & Fly, 2006; Mickleborough, Murray, Ionescu, & Lindley, 2003; Walser & Stebbins, 2008). In a follow-up study, McAnulty et al. (2010) showed that omega-3 PUFA supplementation was associated with an increase in F_{2}-isoprostanes in response to heavy cycling exercise and that supplementation with antioxidant vitamins and minerals does attenuate the increase in F_{2}-isoprostanes but does not increase ferric-reducing antioxidant potential. Based on these data it is quite clear that further research is required on whether the potential benefits of omega-3 PUFA supplementation outweigh the potential risks of enhanced lipid peroxidation in athletes engaged in heavy exercise.

While, at present, the limited human data do not support the hypothesis that omega-3 PUFA supplementation is effective in enhancing exercise performance, it has been demonstrated that omega-3 PUFA can affect not only cognitive function but also mood and emotional states (e.g., depression) and may act as a mood stabilizer (Fontani et al., 2005; Silvers & Scott, 2002). Guzman, Esteve, Pablos, Pablos, and Villegas (2011) recently showed that supplementing 24 female elite soccer players with 3.5 g/day of DHA-rich fish oil for 4 weeks produced perceptual-motor benefits (i.e., improvements in complex reaction time and efficiency), which supports the view that DHA may improve performance in sports where perceptual motor activity and decision making are the keys to success (Overney, Blanke, & Herzog, 2008). For example, omega-3 PUFAs may have potential to enhance the decision-making abilities of athletes who engage in sports performed in extreme and stressful environmental conditions (e.g., altitude, extreme heat or cold)

**Omega-3 Fatty Acids and Exercising Cardiac Function**

In a meta-analysis of randomized, double-blind, placebo-controlled human trials, fish-oil supplementation reduced heart rate at rest by 1.6 beats/min (Mozaffarian et al., 2005). This finding in humans confirms experimental studies conducted in isolated rat myocytes, exercising dogs, and nonhuman primates that also suggest that fish oil may have direct cardiac electrophysiological effects including the slowing of heart rate (Billman, Kang, & Leaf, 1997; Leaf, Kang, Xiao, & Billman, 2003; McNemar, 2001). Potential mechanisms such as effects on the sinus node, ventricular efficiency, or autonomic function warrant further investigation. To date there have only been
a few studies conducted examining the effect of fish-oil supplementation on cardiac function during exercise.

Peoples, McLennan, Howe, and Groepler (2008) examined the effects of fish-oil supplementation (8 × 1-g capsules/day of omega-3 PUFA-rich tuna oil or placebo for 8 weeks) on human heart function in well-trained males and found that during exercise (55% of VO2max until voluntary exhaustion) they exhibited significantly lower heart rates, rate pressure product, and whole-body O2-consumption than with placebo. However, a limitation in their study is the lack of a measure of exercise performance. Ninio, Hill, Howe, Buckley, and Saint (2008) showed that intake of 0.36 g/day of EPA and 1.56 g/day of DHA increased parasympathetic measures of heart-rate variability and lowered the heart-rate response to exercise in patients with risk factors for coronary artery disease. That study provides further evidence supporting the use of fish-oil supplementation not only for patients with established coronary disease but also for those at risk for future cardiovascular disease.

Walser et al. (2006) showed that fish-oil supplementation (3.0 g/day EPA and 2.0 g/day DHA) enhances exercise-induced increases in brachial-artery diameter and blood flow during rhythmic handgrip exercise. They speculated that these findings may have implications for patients with cardiovascular disease and exercise intolerance. In a follow-up study, Stebbins et al. (2010) showed that supplementation with EPA and DHA can augment the contraction-induced increases in skeletal-muscle blood flow and conductance in exercising rats, therefore resulting in strong correlations between changes in these two variables and the percent sum oxidative fibers (Types I and IIa) observed in the individual muscles or muscle parts. These augmentations in blood flow and conductance occurred in the absence of any changes in perfusion pressure (i.e., mean arterial pressure) or heart rate. These data indicate that EPA and DHA supplementation may effectively alter vasoreactivity in the vasculature of skeletal muscle. Stebbins et al. speculated that the source of this enhanced skeletal-muscle blood flow is increased cardiac output caused by a decrease in systemic vascular resistance that is concomitant with PUFA-induced increases in muscle conductance.

Omega-3 Fatty Acids and Exercising Animals: Relevance to Human Exercise Performance

Several previous studies suggested that intake of PUFAs may indeed affect the performance of skeletal muscles and locomotion in vertebrates. In Atlantic salmon, for instance, dietary fatty-acid composition and resulting changes in muscle lipid composition significantly affected maximum swimming speed. These effects were largely due to a positive relation between swimming speed and the most common omega-6 fatty acid in muscle lipids, linoleic acid (Mckenzie, Higg, Dosanjh, Deacon, & Randell, 1998). Salmon fed a diet in which menhaden oil furnished the entire supplemental lipid had a significantly lower swimming speed than those fed a diet in which the supplemental lipid was an equal blend of menhaden and canola oil (rich in 18-carbon unsaturated fatty acids). Furthermore, there was a highly significant linear relationship between dietary and/or muscle levels of particular fatty acids or groups of fatty acids and swimming speed (Mckenzie et al., 1998).

In addition, muscles that undergo very high contraction frequencies, such as the pectoral muscle in hummingbirds, contain very large amounts of DHA (Infante, Kirwan, & Brenna, 2001). In humans, training exercise increases muscle PUFA content (Helge et al., 2001). Furthermore, it has recently been found that the proportions of PUFA in the muscle phospholipids of an extremely fast runner, the brown hare (Lepus europaeus), are very high compared with other mammals (Valencak, Arnold, Tataruch, & Ruf, 2003). Based on these findings, Ruf, Valencak, Tataruch, and Arnold (2006) hypothesized that muscle phospholipid profiles may be functionally related to locomotor performance. Their study examined the relationship between total PUFA content, any of the PUFA subclasses, or a particular fatty acid and locomotor function as measured by running speed of 36 mammalian species. The data revealed a strong relationship between the omega-6 PUFA content in muscle phospholipids and maximum running speed in mammals. Ruf et al. speculated that omega-6 PUFAs exert a positive effect on muscle performance and maximum running speed by facilitating Ca²⁺ uptake into the sarcoplasmic reticulum by increasing the activity of sarcoplasmic Ca²⁺ Mg²⁺-ATPase (Ushio et al., 1997).

Lortet and Verger (1995) investigated the cardiac function of anesthetized rats after the administration of three different diets enriched in saturated fat (lard), omega-6 PUFA (sunflower oil), or omega-3 PUFA (fish oil) at baseline and after a moderate sustained exercise bout. The animals who consumed the fish-oil diet exhibited changes in hemodynamic parameters (20% reduction in left-ventricular pressure, maximal rate of rise in pressure [LVdP/dtmax], mean aortic pressure, and heart rate and a 30% reduction in LVdP/dtmin) compared with the animals who consumed the other diets, but only when they participated in the moderate exercise-running protocol. Lortet and Verger speculated that the increased production of endothelium-derived relaxation factor and/or a decrease in blood viscosity could explain their results. Demaison, Blet, Sergiel, Greire, and Argaud (2000) found that rats consuming fish oil had reduced heart rate, aortic flow, and cardiac output due to a decrease in vascular resistance. Similarly, O’Connor et al. (2004) found that thoroughbred horses administered fish oil for 63 days had lower heart rates and packed-cell volume during exercise than horses fed corn oil.

The endurance capacity of long-distance migrants has fascinated scientists for many years. Recent work has attempted to unravel the physiological mechanisms that underlie their athletic performance. Because of their extreme athletic accomplishments, migrant birds have recently received attention as models for studying...
the effects of dietary PUFAs on exercise (Price, 2010). Modern tracking using satellite technology has shown that annual round-trip flights of more than 64,000 km are not uncommon in some marine birds (Shaffer et al., 2006). The activities of marker enzymes for flux capacity through the citric acid and β-oxidation cycle have been measured in several species of migrant birds. As anticipated, the oxidative capacity of their flight muscles is higher than that of sedentary species (Bishop, Butler, Egginton, el Haj, & Gabrielsen, 1995; Suarez et al., 1990), and it is further enhanced seasonally at the time of migration (Guglielmo, Haunerland, Hochachka, & Williams, 2002; Maillet & Weber, 2007).

Recent research reveals that some migrant birds use components of their diet as performance-enhancing substances to achieve a large increase in aerobic capacity just before departure. This form of “natural doping” was discovered in semipalmated sandpipers (Calidris pusilla L.) preparing for the longest nonstop flight of their annual cycle, which is an approximately 4,500-km transatlantic trip from eastern Canada to South America requiring a 3-day flight at approximately 60 km/hr (Guglielmo et al., 2002; Maillet & Weber, 2006, 2007). While refueling in the Bay of Fundy (New Brunswick, Canada), these sandpipers double their body mass from approximately 20 to 40 g by feeding on small burrowing amphipods (Corophium volutator Pallas) that contain very high levels of omega-3 PUFAs. This activity is noteworthy since the fatty-acid composition of artificial diets has been shown to influence the capacity for endurance exercise in a variety of animals including rats (Ayre & Hulbert, 1997), Atlantic salmon (Salmo salar L.; Mckenzie et al., 1998), and the red-eyed vireo (Vireo olivaceus L.), a migrant songbird (Pierce, McWilliams, O’Connor, Place, & Guglielmo, 2005).

EPA and DHA account for 45% of total lipids in the diet naturally consumed by the semipalmated sandpiper. Therefore, it seems these birds enhance the aerobic capacity of their flight muscle by eating large amounts of omega-3 PUFAs that are known to cause pharmacological-like effects in mammalian cells in vitro. While the exact molecular mechanisms are unknown, natural doping appears to influence the capacity for endurance exercise in a variety of animals including rats (Ayre & Hulbert, 1997), Atlantic salmon (Salmo salar L.; Mckenzie et al., 1998), and the red-eyed vireo (Vireo olivaceus L.), a migrant songbird (Pierce, McWilliams, O’Connor, Place, & Guglielmo, 2005).

Conclusion

While a number of studies have assessed the efficacy of omega-3 PUFA supplementation on exercise performance, power, muscle damage, inflammation, and metabolism during exercise, there are only a limited number of studies that evaluated the impact of omega-3 PUFA supplementation on exercise performance. This review has shown that, at present, the human data are inconclusive as to whether omega-3 PUFA supplementation is effective in attenuating the inflammatory and immunomodulatory response to exercise and thus could enhance subsequent exercise performance. It is clear that further studies are needed to provide unequivocal proof of this effect. The inconsistency among study results may be due to the heterogeneity in (a) definitions of setting (field vs. laboratory test), mode, intensity, and duration of the exercise test used to assess performance; (b) definitions of populations (e.g., age, gender, untrained vs. trained individuals); (c) interventions and their contrasts with comparators (e.g., different types and amounts of fish oil and omega-3 PUFAs used); (d) the dosage and duration of omega-3 PUFA-supplementation variation among published studies; and (e) the timing of the measurements and selection of biomarkers among studies. Future studies investigating the efficacy of omega-3 PUFA supplementation in exercise-trained individuals should consider using an exercise protocol of sufficient duration and intensity to produce a more robust oxidative and inflammatory response.

However, animal studies assessing the effectiveness of omega-3 PUFA supplementation on exercise metabolism and endurance exercise performance have produced very promising findings. Based on the current literature, future studies in humans should focus on assessing the effectiveness of omega-3 PUFA supplementation on DOMS and subsequent exercise performance in athletes (e.g., multisport) and military personnel who typically engage in more than one workout per day using a more robust research design than those that have been used in previous studies. In addition, based on data generated from long-distance migrant birds (Maillet & Weber, 2006, 2007), it would be of interest to assess the impact of omega-3 PUFA supplementation on exercise metabolism and endurance exercise in untrained versus trained individuals.

While the use of supplemental omega-3 PUFAs has been indicated to improve performance in laboratory animals and migrant birds, and to a limited extent in humans, it has not been definitely proven, and thus, at the present time, it is difficult to make any firm recommendations to athletes regarding the amount and duration of omega-3 concentrations of FABP that accelerate lipid transport, and by boosting the metabolic machinery for lipolysis in adipocytes and lipid oxidation in muscle mitochondria. Research on the physiology of long-distance migrants may have important implications for the not only treatment of obesity but also for improving the performance of human athletes.
Some species of fish are known to be contaminated with toxins such as heavy metals, dioxins, and PCBs. Fish-oil supplements are made from these fish and may retain these contaminants unless they have undergone molecular distillation to purify them. Most studies that have looked at reputable brands of fish-oil supplements have not found significant levels of contamination. Pharmaceutical-grade fish oils should be free of these contaminants (Krist-Etherton, Grieger, & Appel, 2009).

One potential side effect of fish-oil supplements is an increased risk of bleeding and immunosuppression (Meydani et al., 1991; Ryan et al., 2009). Because fish oils decrease the stickiness of blood platelets, they decrease clot formation and can increase the tendency to bleed. This is unlikely to be a problem at low doses, but there is some evidence that high doses may increase the risk of hemorrhagic stroke (Krist-Etherton, Harris, & Appel, 2002).

Fish oils are known to cause a variety of digestive problems including flatulence, bloating, acid reflux, nausea, and diarrhea (Krist-Etherton et al., 2002). This can sometimes be prevented by taking fish-oil supplements with meals and starting with a low dose.

Although fish oils have been shown to lower triglyceride levels, as well as protect against heart disease, higher doses may increase LDL cholesterol by up to 10% (Krist-Etherton et al., 2002). However, more research needs to be conducted in this area.

Fish-oil supplements have been demonstrated to lower blood pressure, which could be a problem for individuals who already have low blood pressure (Mori & Beilin, 2001).

Some individuals have reported a “fishy taste” in their mouth after taking fish-oil supplements (Krist-Etherton et al., 2002).

Attempts should be made to establish an optimal omega-3 PUFA dosage to maximize the risk-to-reward ratio of supplementation. It has been suggested that for most athletes, ingesting approximately 1–2 g/day of EPA and DHA at a ratio of EPA to DHA of 2:1 would be beneficial in counteracting exercise-induced inflammation and for the overall health of an athlete (Simopoulos, 2007). However, it should be noted that an omega-3 PUFA (EPA+DHA) dose of ≤3,000 mg/day has been designated as safe for general consumption by the U.S. Food and Drug Administration (2004), and it is recommended that athletes abide by this recommendation if consuming fish oil to decrease muscle soreness or pain from exercise.

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