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Review Article

Omega-3 Supplementation is Effective in Reducing Interleukin-6 Levels After Physical Exercise: A Systematic Review

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ABSTRACT

Not only does physical exercise improve health, it can also trigger inflammation. Therefore, supplementation after exercise is necessary to reduce it. Omega 3 is one of the nutrients that can potentially reduce inflammation. The fundamental however, the mechanism is not well known. This study examined how omega-3 supplementation while exercise affected IL-6 levels, an inflammatory biomarker. Our systematic review analysis examined interleukin 6, inflammation, and omega 3 papers from Pubmed, Web of Science, and Science Direct during the previous five years. This systematic review assessed nine eligible papers. This research assessed standard operating procedures using PRISMA. Taking omega-3 supplements while working out has been shown to reduce IL-6 levels. IL-6 is reduced by omega-3 supplementation during exercise. So, this can be a recommendation for sportsmen in routine consumption to prevent inflammation during exercise.

Introduction

High-intensity eccentric muscular contractions cause exercise-induced muscle damage (EMID) [1]. Due to increased inflammation, delayed onset muscle soreness (DOMS) from EIMD affects muscular strength, range of motion, and performance [2]. EIMD-induced muscle injury raises inflammatory biomarkers such as TNF-α, IL-6, IL-1, and CRP [3]. Physical activity increases nuclear transcription factor kappa beta (Nf-kB), which is impacted by ROS [4]

Myokines, signaling molecules released by skeletal muscles during exercise, benefit muscles and the body via endocrine, paracrine, and autocrine pathways [5]. High amounts of inflammatory cytokines like interleukin-6 (IL-6), which has several physiological and pathological activities, cause tissue inflammation. IL-6 is crucial to acute inflammation, especially in severe infections [6]. It also indicates viral infection [7]. persons with metabolic problems including type 2 diabetes, obesity, and chronic inflammatory illnesses like rheumatoid

arthritis have higher IL-6 levels than healthy persons [8]. During exercise, levels of IL-6, a family of myokines increase 100-fold in the blood circulation physiologically, this is as a physiological response to exercise, then IL-6 will produce a spike in the systemic, but immediately after the exercise session will return to normal levels by itself after recovery [9]. Furthermore, during physical activity, IL-6 functions as a metabolic regulator between organs by stimulating the liver to produce more glucose [10]. Liposolysis in adipose tissue is also promoted [11]. Muscle function is enhanced during single resistance exercise because the rise in IL-6 during exercise also makes it easier for muscle fibers to absorb and catabolize energy sources, such as glucose and fatty acids [12].

During physical exercise it will trigger an increase in contraction of the skeletal muscles [13]. In addition, IL-6 is produced as a "myokine" by skeletal muscle contraction; in this role, IL-6 seems to increase during exercise, studies in rats have shown to increase IL-6 when given physical exercise interventions, perhaps this increase is due to the formation of a larger energy system [14]. Which will then trigger the emergence of the training adaptation process [12]. However, in the context of exercise, IL-6 synthesis has been linked to more severe kelelahan and has been recommended to be used in a variety of exercise-related disorders [15]. However, research has demonstrated that increasing ROS causes oxidative stress (OS) to follow EIMD [16]. In this sense, exercise, which triggers acute OS and inflammatory reactions, can also control endogenous antioxidants [17]. Because OS and the inflammatory process are both directly engaged in EIMD, they must be examined and managed in tandem [18]. One strategy to lessen EIMD and avoid or reduce the consequences of OS and inflammatory processes [19].

Additional vitamins are needed to avoid exercise-related inflammation. People need omega-3 polyunsaturated fatty acids. Animal sources of DHA and EPA are more absorbable [20]. Salmon, mackerel, sardines, and tuna oil contain EPA and DHA. The body easily absorbs and utilizes long-chain omega-3 fatty acids from these marine fish [21]. Omega-3 fatty acids EPA and DHA may benefit eating disorder sufferers. Metabolic syndrome, CVD, NAFLD, diabetes, and obesity benefit from omega-3 supplementation [22]. DHA and EPA supplementation improved oxidative-antioxidative, lipid, and carbohydrate metabolism indicators, suggesting modulatory and anti-inflammatory effects [22]. For instance, EPA and DHA may reduce pro-inflammatory indicators including TNF-alpha, COX-2, IL-6, IL-8, and IL-1β [23]. Numerous studies have shown that n-3 PUFAs may also help people of different ages who regularly engage in physical activity levels maintain or improve their muscle strength [24]. Omega 3 supplementation in reducing inflammation during exercise is still not fully understood. In addition, the underlying mechanism is also not clearly understood. Therefore, this systematic review will discuss how taking an omega-3 supplement while exercising affects IL-6, one of the inflammatory indicators.

Subjects and Methods

Study Design

Researchers examine PubMed, Web of Science, and ScienceDirect for a comprehensive. Scientifically strong and influential publications are best collected on these venues. In the first search, duplicate articles are removed, and predetermined inclusion and exclusion criteria are used to filter.

Eligibility criteria

The inclusion criteria the research based on five-year reviews of studies on exercise, omega-3 supplementation, inflammation, and IL-6 release. We also rejected papers that were not indexed in Web of Science, PubMed, or ScienceDirect or did not fulfill scientific validity requirements.

Procedure

Full articles, abstracts, and titles were uploaded to Mendeley after verification and approval. The first step found 145 papers using Web of Science, PubMed, and ScienceDirect. After the second screening, 107 articles satisfied the requirements based on title relevance. After assessing titles, abstracts, and keywords, 52 articles were selected in the third round. In the last step, we carefully examined all the papers and verified that the research sample should include people, be original, focus on IL-6, contain omega-3 supplementation, and include physical activity. We sorted articles by relevancy. Nine publications that matched inclusion criteria were analyzed after a comprehensive examination. PRISMA guidelines were used for operational criteria.

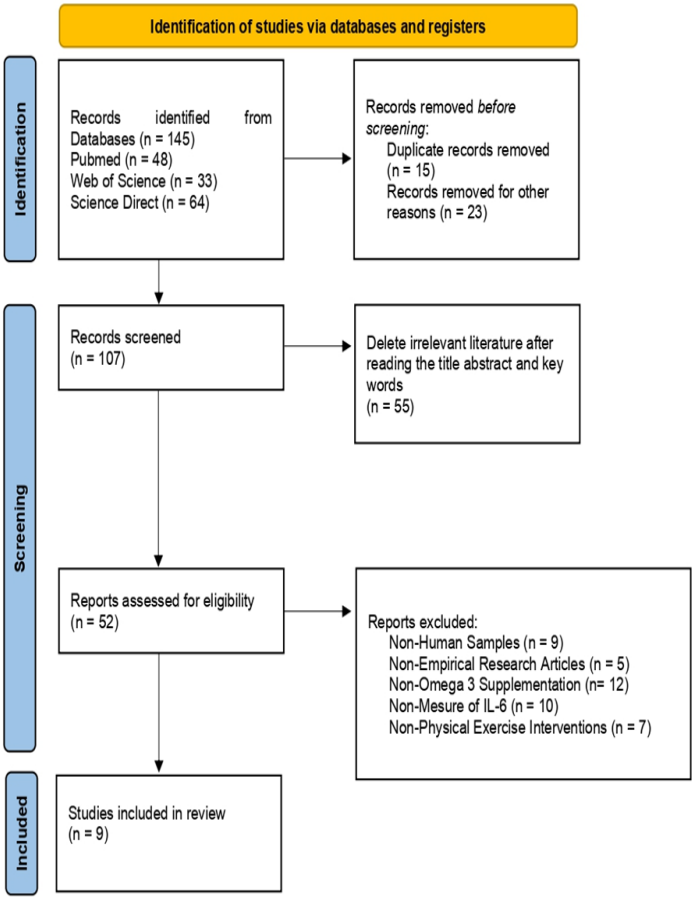

Figure 1: PRISMA flowchart of the article selection process

Results

The design and intervention of the studies that were eligible for inclusion are summarized and listed in table 1

Table 1. Summary of the design and intervention of the studies

Author	Design	Participants	Participants Age	Intervention	Outcome
(Barquilha et al., 2023) [25]	Randomized controlled trial	21 healthy men	20-30 years old	Pre-workout and six weeks post-workout phases of training, a single strength training session was implemented, consisting of six sets of no more than ten repetitions with a one-minute break in between sets. In summary, the participants followed the following training plan: 6 sets of 10 reps with 1-minute intervals (6×10 with 1-minute intervals) for weeks 1, 3, and 6 (hypertrophy); 5×5 with 3-minute intervals for weeks 2 and 4 (strength); and 2×20 with 1-minute intervals for week 5 (resistance). The participants received three fish oil capsules daily, including 606 mg of DHA and 780 mg of EPA. Six weeks of supplementation were administered.	The group receiving an omega 3 + physical exercise intervention saw a significant drop in IL-6 levels.
(Tsuchiya et al., 2021) [26]	Randomized controlled trial	22 healthy recreational untrained men	19-20 years old	The fitness regimen lasted four weeks. Participants sat on a preacher curl bench with shoulder joints at 45° flexion during eccentric contraction. Maximal voluntary contraction torque at 90° was translated to kg for dumbbell usage. Participants did six sets of 10 maximum elbow flexor eccentric contractions, with a 90-second rest period between sets. After releasing the dumbbell, participants returned their arm to the starting position for the next eccentric contraction. Participants took eight softgel capsules containing 300 mg of EPA-rich fish oil daily, totaling 2,400 mg (600 mg EPA, 260 mg DHA). The supplementing phase lasted four weeks.	The omega 3 intervention group's IL-6 levels significantly decreased. The IL-6 reduction peaked on the second day following the exercise intervention.
(Mullins et al., 2022) [27]	Randomized controlled trial	38 football player	-	As usual, participants train for soccer. The intervention lasted for twenty-six weeks. Participants in the treatment group were told to consume 3.5 g of DHA+EPA daily.	There was a significant reduction in IL-6 levels after 26 weeks of intervention.
(Kyriakidou et al., 2021) [28]	Randomized controlled trial	23 healthy, physically active males	18-35 years	Research participants ran downhill for 60 minutes at 65% VO2max on a -10% gradient as part of the EIMD protocol. During the study, RPE and HR were recorded every ten minutes. Participants were seated and blood samples were taken right after the muscle-damaging bout (post-EIMD). After rating their perceived level of muscle discomfort, participants' strength and power output were evaluated using the Wingate and MVIC tests, respectively, following EIMD. Omega 2 supplementation (3 g/day of n-3 PUFA) was carried out.	Twenty-four hours following the EIMD session, IL-6 levels significantly decreased.

				Omega-3 supplementation included three gelatin-coated capsules daily (one taken in the morning, one at lunch, and one at night). Participants took 3900 mg of fish oil daily, each capsule containing 1040 mg of n-3 PUFA, comprising 715 mg of EPA and 286 mg of DHA. Each pill included 3g of n-3 PUFA for four weeks.	
(Ha et al., 2022) [29]	Randomized controlled trial	Sixty-one participants	65-85 years old	Participants received weekly vibration training on a Galileo® side-change plate under organization supervision. The training consisted of three minutes of 1.5-2 mm dynamic and static squats, a one-minute warm-up at 12 Hz. Every participant was also given instructions for three times a week of resistance exercise at home. In these approximately 45-minute sessions, participants completed three sets of bodyweight exercises including sit-up. The doctor advised taking 3.5 mL of algal oil daily with high-fat meals.	The group receiving omega-3 supplementation showed a significant reduction in IL-6 levels.
(Lee & Directo, 2023) [30]	Randomized controlled trial	Twenty healthy older women	65 years old	For eight weeks, every participant engaged in twice-weekly resistance exercise. For the five main upper and lower body muscular groups (leg press, calf raise, biceps curl, seated row, and lat pull-down), the exercise program comprised three sets of twelve repetitions or until failure, whichever occurred first. To guarantee correct execution and reduce the chance of damage during resistance training sessions, study team members actively monitored the training sessions. The beginning exercise intensity was 50% of 1 RM. The training load was raised by 5% each week if the individual performed the recommended effort, reaching 70% of 1 RM by the second week to produce adaptive hypertrophic response. If participants are unable to complete 10 RM, the load is carried over to the following session. Each training session started with stretching and low-intensity activities Omega-3 supplement included DHA (0.24 g) and EPA (0.7 g). For a daily total of 0.72 g DHA and 2.1 g EPA, the supplement group consumed three fish oil capsules, one with each meal.	There is a significant decrease in IL-6 in those that consume omega-3 fatty acids and exercise.
(Domingo J et al., 2020) [31]	Randomized controlled trial	Fifteen healthy male amateur endurance athletes	18-45 years	Using a multipowe machine, athletes completed eight sets of six half squat repetitions at 110% of 1-RM during the training session, with two minutes of rest in between sets. Two assistance lifted the weight to begin the subsequent repetition, but the athlete only executed the eccentric phase. The athletes had three seconds to drop the weight. The Borg scale assessed the athlete's felt effort (RPE) after completing the activity. Participants completed 8 sets of 10 drop vertical leaps on a 60 cm platform, taking a 1-minute break sets and five minutes after completing the last half-squat exercise. The athletes were told to jump as high as they could as soon as they were off the box. Volunteers consumed either PLA (500 mg olive oil placebo) or six DHA + EPA soft gels (Brudy Plus, Brudytechology, Barcelona, Spain), all of which looked the same. A DHA + EPA soft gel the study included taking	Following exercise and omega-3 therapies, IL-6 levels dramatically dropped. Twenty-four hours following activity, the omega-3 fatty acid level peaked.

				a single dosage of 2.34 g of total omega-3 PUFA fatty acids in the morning before breakfast for 10 weeks.	
(Jaworska et al., 2023) [32]	Randomized controlled trial	Twenty-four male long-distance runners	33-35 years	The eccentric workout regimen (downhill run) is finished by the participants. Using a treadmill that was adjusted to run backwards on a -16% gradient, each participant ran downward for 30 minutes. After three minutes, the pace was raised until an HR equal to 70% VO2max was attained. The test started at 6 km/h. It has been proposed that following a downhill run, this regimen causes a considerable amount of muscle injury. Participants took six capsules of 3,000 mg concentrated fish oil (three in the morning and three in the evening) or six capsules of gelatin (three in the morning and three in the evening) made by the same company for three weeks.	The intervention of omega-3 and physical activity significantly reduced IL-6 levels.
(Haß et al., 2023) [33]	Randomized controlled trial	Sixty-one participants	65-85 years	Weekly vibration training on alternating vibration plates is provided to all participants. This included three minutes of 1.5–2 mm amplitude dynamic and static squats frequency of 12 Hz, and a one-minute cool-down with a frequency of 12 Hz. Every participant was also given instructions for three times a week of resistance exercise at home. During these roughly 45-minute sessions, participants performed three sets of body weight exercises sit-up crunches. At baseline, each participant's vibration of repetitions of the workouts were assessed separately to take into consideration their physical condition and prevent under- or over-exercising throughout the intervention period. Each participant's training program started at their personal maximum performance level and advanced each week by increasing the vibration (+2 Hz) and repetition count (+2). Compliance with the training protocol was documented in a training journal. The protein + omega-3 group received 3.5 mL of algal oil daily, including 2,195 mg Omega,1,397 mg DHA, 749 mg EPA, and 49 mg docosapentaenoic acid). The plasma omega-3 index assessed to determine compliance at the conclusion of the research.	There was a significant decrease in IL-6 levels in the omega 3 intervention group.

Discussion

This research examined how omega-3 supplementation after exercise affected interleukin-6 levels, an indication of inflammation. The investigation showed that omega-3 supplementation during exercise significantly reduced IL-6 levels, an inflammatory biomarker. The previous research found that 780 mg EPA and 606 mg DHA supplementation during interval physical exercise for 6 weeks effectively reduced IL-6 levels [34]. Earlier study showed that 300 mg of fish oil per day and 4 weeks of weight training lowered IL-6 levels [26]. Other studies demonstrate that soccer players supplementing with 3.5 g DHA + EPA 5 times a week for 26 weeks reduced IL-6 levels [27]. Omega-3 supplementation after exercise significantly lowers IL-6, an indicator of inflammation.

The results of earlier research indicates that physical activity causes muscle damage in the form of downhill running which is done 60 minutes with 65% VO2max by giving omega 3 supplementation at a dose of 3 grams given for 4 weeks is significantly proven to reduce IL-6 levels [28]. Other research results omega 3 intervention provided by doing home-based resistance training and performed 45 minutes per session 3x a week which includes marching, squats, chair lifts, chair dips, and three rounds of sit-up crunches proved significant in reducing IL-6 levels [29]. The outcomes of previous research omega 3 supplementation given while doing programmed resistance training consisting of leg press, calf raise, biceps curl, seated row, and lat pull-down performed twice a week for 8 weeks significantly reduced IL-6 levels [30]. It also supports the discovery that omega 3 supplementation during IL-6 levels may be significantly reduced by exercise following the intervention [35]. The research found that omega-3 supplementation during exercise significantly lower IL-6. Further is needed how to omega-3 supplementation affects IL-6 levels after exercise.

Physical Exercise Increases Interleukin-6

Low-molecular-weight proteins called cytokines control hematopoiesis, inflammation, and immunity. Numerous cells, including as fibroblasts, endothelial cells, immunological cells, and

other stromal cells, generate them. Stromal cells to control hematopoiesis, inflammation, and immunity [36]. Cytokines are classified into family groups based on their secretion from secondary and tertiary structures or cells [37]. Immunomodulatory IL-6 has several physiological impacts. Pro- and anti-inflammatory cytokines may rise with exercise. Regular moderate exercise is essential for mental and physical health; nevertheless, severe exercise is associated with transient immunosuppression, which may be caused by higher cortisol levels or inhibitory cytokines after hard exercise [38]. Furthermore, it is believed that intense exercise suppresses cellular immunity [39]. According to Gill et al., 2015 blood samples taken from competitors showed that there was transient bacteremia following severe endurance sports.

Epidemiological research has identified a link between the amount of physical activity and the strength of the body's immune. Skeletal releases IL-6 into interstitial systemic circulation during exercise, which redirects energy to contracting muscles through endocrine, autocrine, and paracrine processes [41]. During exercise, plasma IL-6 concentrations rise exponentially and peak at the conclusion of the workout [42]. Circulating IL-6 increased most when exercise was done for longer periods of time, utilizing larger muscle groups and at greater intensities [43]. IL-6 from muscles has a five-minute half-life and is removed from plasma after exercise because skeletal muscle synthesis decreases and hepatic clearance increases [44]. After vigorous exercise, muscle damage increases cytokine expression, resulting in elevated muscle IL-6 levels [45]. In another research, energy substrates increase IL-6 levels, which may explain athletes' higher IL-6 levels [46].

Omega 3 Supplementation During Physical Training Lowers Interleukin-6 Levels

The Greenland Eskimos, whose fish-rich diet reduced multiple sclerosis, asthma, type 1 diabetes, and coronary heart disease, first promoted omega-3 fatty acids like EPA and DHA (Patted et al., 2024). Omega-3s are needed for cell membrane development and receptor function, according to many studies. Lipids are the principal source of clotting, inflammation, and arterial contraction and relaxation hormones. Additionally, these lipids may bind to cell receptors that influence genetic activity. Omega-3 fats may prevent cancer, cure lupus, dermatitis, and rheumatoid arthritis, and lessen heart disease and stroke risk [47]. Seals, whales, cod, halibut, salmon, mackerel, and menhaden contain omega-3 polyunsaturated fatty acids. Most fish oils contain minimal DPA, while EPA and DHA are the main marine omega-3s [48].

Omega 3 has numerous double bonds [49]. Most omega-3 fatty acids consist of DHA, EPA, and ALA (50). Omega 3's anti-inflammatory properties are well known **51**. Additionally, research has shown that omega-3 supplements help preserve muscle function and alleviate pain following muscle damage caused by eccentric exercise **52**. By reducing TNF-α release, omega-3 fatty acids affect cytokine secretion, which in turn affects the immunological response [53]. By inhibiting TNF-α signals and triggering muscle protein reactions, omega 3 can reduce inflammation [54]. Gutiérrez-Pliego et al. (2018) suggest may reduce TNF-α levels [55]. The results of the study (Coghill et al., 2018) reported that Omega-3 can reduce CRP and IL-6 because omega 3 contributes to the uncontrolled inflammatory process, so it will naturally reduce discomfort [56]. Research result from Corder et al., 2016 illustrates how taking supplements can improve muscle strength and lessen the severity of pain. Omega 3 can enhance mitochondrial activity by integrating into mitochondrial membranes [57]. Because omega 3 supplements lower the cost of oxygen, they may increase aerobic endurance, particularly at submaximal workloads [58], and can even to an increase in VO2max [59]. Increased muscle protein synthesis has been shown in studies examining how omega 3 affects muscular strength [60] and the possibility of gaining more strength in adults [60],[61]. Omega 3 supplements work well for hyperinsulinemia and hyperaminoacidemia in young, healthy persons [62].

Acute inflammatory responses reduce damage and infection risk via cellular and molecular interactions. This reduces acute inflammation and restores tissue homeostasis. Acute inflammation may become chronic and cause inflammatory illnesses if not controlled [63]. The total inflammatory response decreases. These metabolites reduce inflammatory cell invasion, suppress proinflammatory cytokines, and help remove cellular debris to stop the inflammatory process. For example, EPA-derived resolvin E1 reduces proinflammatory cytokines by inhibiting the NF-κB pathway, a critical regulator of inflammation [64]. Through prolonged inflammation, this mechanism may also cause neurodegeneration [65].

Omega-3 fatty acids may also increase myogenesis [66]. Nuclear receptors termed peroxisome PPARs regulate satellite cells, facilitate skeletal muscle adaptation after exercise, and prevent metabolic disorders [67]. PPARs regulate genes required for inflammation, lipid and glucose metabolism, and development. Research suggests omega-3 acids activate PPARs and change inflammation-regulating gene expression [68]. Omega-3 also decreases cytokine and inflammatory protein production, including TNF-α and IL-6, and NF-kB activation. When inflammation is reduced, satellite cells proliferate and differentiate more in muscle [66]. Research indicates that omega-3 supplementation and exercise may reduce inflammation by lowering CRP, IL-1, IL-6, IL-10, and TNF-α. This reduction in inflammation alleviates pain, which subsequently enhances performance during exercise programs, especially those focused on muscle building [69].

Strength and Limitations

The samples used were human-based, ensuring that the data is homogeneous and not mixed with animal samples like those from mice or other animals.

However, a limitation of the review is the lack of discussion on how omega-3 supplementation during exercise reduces IL-6 levels, which are a key marker of inflammation. Therefore, conducting further research on this topic is crucial to deepen our understanding of how omega-3 supplementation impacts IL-6 levels during physical activity, as well as to explore the underlying mechanisms. Such studies could provide valuable insights and recommendations for athletes to incorporate omega-3 supplements as part of their nutrition strategy.

Conclusion

According to the evaluated publications, omega-3 supplementation during exercise reduces IL-6 levels, which indicate inflammation. However, the appropriate dose to reduce IL-6 during

exercise is unknown. Thus, further study is needed to establish the best dosage.

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Conflict of Interest

Authors declare no conflict of interest.

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