INFORMATION PAPER ON OMEGA-3 SUPPLEMENTS FOR MILD TRAUMATIC BRAIN INJURY

KEY TAKEAWAY

The pre-clinical evidence reviewed in this information paper supports the potential prophylactic benefit of omega-3 (O3) fatty acids for improving cognitive functioning following mild TBI. However, this evidence has not been sufficiently replicated in clinical studies, which involve complex human factors that are more challenging to control than in preclinical trials. Supplementation of up to 5 grams of omega-3 fatty acids is generally considered safe for healthy individuals, but the extent to which this recommendation applies to warfighters recovering from mild TBI requires further study.

PURPOSE

The purpose of this information paper is to provide a general overview of the current state of the science on the use of omega-3 supplements for the prevention and treatment of mild TBI.

The information provided herein is current as of March 2025 and is subject to change given emerging peer-reviewed research and evidence.

BACKGROUND

It is well documented that several pathophysiological processes can occur following mild TBI, including the breakdown of cellular homeostasis, ineffective oxidative metabolism and increased oxidative stress, mitochondrial dysfunction, axonal damage, and neuroinflammation.[1] These physiological changes occur secondary to the initial physical head trauma,[1] and likely contribute to symptoms that arise in the weeks, months, and years following the injury. Despite knowledge of these mechanisms of secondary injury, there are no FDA-approved pharmaceuticals for the treatment of TBI neuropathology.[2] To fill this gap, many are turning to nutritional interventions to both prevent and treat TBI. Omega-3 fatty acids are among the most commonly researched nutrients for these purposes.[3,4]

Omega-3 fatty acids are long chain polyunsaturated fatty acids. There are four major omega-3 fatty acids: alpha linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). ALA is a precursor of DHA and EPA,[5] and DPA is an intermediate metabolite between EPA and DHA.[6] ALA is found in plant-based foods, such as flaxseeds, walnuts, and plant-based oils, and is an essential fatty acid,[7,8] meaning it is obtained exclusively through the diet.[9] DHA and EPA are nonessential fatty acids as they can either be synthesized within the body from ALA or obtained through the diet primarily though animal-based foods such as salmon or other fatty fish.[7,8] ALA, DHA, and EPA can be consumed naturally through animal or plant-based foods, can be added to foods such as juices and eggs through fortification, or can be consumed in supplement forms.[7] The in vivo conversion of EPA and DHA from ALA is inefficient, with an estimated 5-10% or less of ALA converted to EPA and DHA;[5,10] thus, adequate dietary intake of omega-3 fatty acids is important to ensure individuals meet daily requirements to maintain normal cellular processes.

Omega-3 fatty acids are fundamental components of neuronal cells that support membrane fluidity, cell signaling, and synaptic plasticity.[11] These fatty acids are thought to protect against neuronal cell death by promoting the production of brain-derived neurotrophic factor,[12] a protein that contributes to neuronal cell body and synaptic growth, dendritic branching, and learning and memory.[12,13] Both DHA and EPA have anti-inflammatory effects through targeting receptors that inhibit the activation of pro-inflammatory macrophages and the production of pro-inflammatory cytokines and free radicals.[14-16] DHA accounts for approximately 10% of the total lipid content of the brain[5] and plays an essential role in neural cell membrane structure and function.[5,17] Diets high in omega-6 (O6) fatty acids promote neuroinflammation, while diets high in omega-3 fatty acids are considered anti-inflammatory.[18] A common metric used to evaluate the inflammatory state is the ratio of omega-6 to omega-3 fatty acids. Most consider 1:1 to be ideal; an imbalance that favors omega-6 fatty acids can lead to neuroinflammation and has been linked to an increased risk of neurodegenerative disease development.[19] Thus, individuals with an adequate intake of omega-3s and a low O6/O3 ratio likely have better health outcomes due to the promotion of anti-inflammatory processes.

DISCUSSION

Omega-3 Fatty Acids and Mild Traumatic Brain Injury

Several clinical biomarkers have been studied to assess the relationship between mild TBI and omega-3 fatty acids including the omega-3 index, metabolites of omega-3 fatty acids, and genotypes of apolipoprotein. The omega-3 index, or O3I, is a measure of the percentage of DHA and EPA bound to red blood cells, is a common clinical biomarker used to assess omega-3 nutrient status and cardiovascular disease risk,[18,20,21] and is correlated with total brain DHA levels.[22] An optimal O3I is greater than or equal to 8%, which indicates a low risk for cardiovascular disease and other adverse health outcomes,[23] while an O3I less than 4% is considered high risk and an O3I between 4-8% is considered moderate risk.[22] Importantly, an optimal O3I for TBI has not been established. Several studies show through plasma phospholipid profiling that individuals with a history of mild TBI have a significantly lower level of omega-3s.[24,25] Further, oxylipins and anandamide, which are metabolites of omega-3 phospholipids and are linked with neuroregulatory processes and anti-inflammatory effects, have shown a correlation with post-concussion symptom severity in U.S. soldiers who sustain a mild TBI.[26] There is evidence that lipid metabolism and the underlying processes of inflammation and oxidative stress after mild TBI is mediated by apolipoprotein polymorphisms.[26-28] Future studies may benefit from controlling for individual genetic differences that have shown an association with plasma omega-3 fatty acids.

Some studies have observed that individuals at high risk for repetitive head injury, particularly athletes and warfighters, fail to meet the target O3I of at least 8%,[23,29-32] despite some considered to have an adequate dietary and supplemental intake of omega-3s.[18,33] A cross-sectional study (n=404) indicated that 34% of Division I football players (n=138) had an O3I of less than 4%, which is considered high risk for cardiovascular disease.[23] No athletes in this study had an O3I above 8%. A small prospective cohort (n=16) study including collegiate Division I soccer players found that the average O3I from pre- to post-season was 3.95%, and the change in O3I over the course of the season was negatively correlated with the frequency of heading the ball.[30] In addition, researchers observed Australian Army recruits (n=117) to have a significantly

lower O3I after 12 weeks of basic training, which may be due in part to having a limited availability of food options with omega-3s during training.[32] Among U.S. soldiers returning from deployment (n=351), 50.5% had an O3I less than 4%, and despite some taking omega-3 supplements (n=97), only five soldiers were considered to have a low-risk O3I.[18] Dosage of omega-3 supplements taken was not provided in this study, and potential variance between soldiers' dosages may explain the low percentage of soldiers considered to have a low-risk O3I. While these findings collectively suggest that those who are at a high risk of head injury may have low omega-3 intake, these studies are limited by a lack of appropriate control groups for comparison. This is an important limitation to determine the true impact of head injury risk on omega-3 status because the general U.S. population is estimated to have an average O3I of 5%, which is already below the recommended value.[34]

Omega-3 blood concentration has also shown some correlation to mild TBI symptomology and cognitive performance. Compared to males with a lifetime history of mild TBI and a high red blood cell concentration of omega-3s, males with a lifetime history of mild TBI and a low red blood cell concentration of omega-3s have reported a significantly higher burden of total post-concussion symptoms, including anger/irritability fatigue, apathy/lethargy, restlessness, and confusion.[25] Another observational study also suggests that elevated serum levels of DHA derived oxylipins during the first three days following an mild TBI may be associated with chronic post-traumatic headache.[35] Furthermore, service members in a deployed setting with a high O3I perform better on executive functioning and cognitive flexibility tests than those with a lower O3I.[36] Given these findings and the known metabolic role of omega-3 fatty acids, research suggests that adequate intake of these fatty acids may reduce the pathophysiological effects that occur after brain injury while also protecting against injury-related decrements in cognitive functioning, thus acting as both a potential therapeutic and prophylactic, or preventative, intervention for mild TBI and a method for optimizing cognitive performance.[36,37]

Prophylactic Use of Omega-3 Fatty Acids

It is well documented that omega-3 fatty acids play a role in decreasing neuroinflammation and oxidative stress, and therefore have been investigated as a prophylactic treatment for mild TBI. While the majority of research on omega-3s has been conducted in preclinical animal models, some clinical studies have evaluated the use of omega-3 supplements as a prophylactic treatment for minimizing the pathology and improving outcomes from mild TBI and subconcussive head impacts.[3] Molecular biomarkers are one area of exploration in the prophylactic use of omega-3 fatty acids for mild TBI. Neurofilament light (NfL) chain, an extensively studied molecular biomarker, is indicative of axonal injury with plasma levels that typically begin to increase within the first 48 hours after head injury.[38] To measure the extent to which omega-3s may reduce axonal injury, many studies have measured the change in serum biomarkers, such as NfL.[22,39,40] During the first three days post-TBI, plasma DHA levels have also shown a moderate negative correlation with higher levels of NfL.[22] Nutrition studies indicate that over the course of an American football season, serum NfL levels generally increase from baseline to post-season for all athletes, but those taking daily omega-3 supplements (2,000 milligrams DHA, 560 mg EPA) have significantly lower NfL levels throughout the sport season,[39] with significant differences observed with as little as 2 grams per day of DHA.[40] The timeline of blood collection varies across studies, but significant differences in NfL levels between those receiving omega-3

supplementation and controls have been observed as soon as 27 days after supplementation begins.[39]

Other clinical studies have shown that omega-3 supplementation does not protect against axonal damage.[41,42] In a neuroimaging-based randomized controlled trial of 27 collegiate American football players assumed to be exposed to repetitive subconcussive head impacts, athletes were randomized to receive capsules of 2.44 grams per day DHA and 1.02 grams per day EPA five times per week for seven months, or a placebo.[42] Compared to preseason levels, end of season serum DHA levels were significantly higher in those that received omega-3 supplements. However, while diffusion tensor imaging did not show significant differences in white matter features between the treatment and placebo groups, there was a statistically nonsignificant increase in structural connectivity in the left anterior and superior corticostriatal tracts for those taking omega-3 supplements. Another study indicated no significant difference in NfL levels between American football players exposed to repetitive head impacts taking 3.5 grams of DHA and EPA 5 days per week for 26 weeks and those who received a placebo.[41] It is important to note that participants in many of these studies did not have a clinically diagnosed TBI,[39-42] and despite an association between NfL and mild TBI, there is no currently accepted threshold for using NfL levels to diagnose mild TBI. While some studies indicate that omega-3 supplements may attenuate axonal injury,[43] it is unclear whether these changes impact post-concussive symptom presentation. To determine the clinical impact of omega-3 fatty acids, future studies should quantify head injury exposure and correlate biomarker data with symptoms and impairments to evaluate whether the results from these exploratory studies are clinically meaningful.

Omega-3 Fatty Acids and Psychological Health and Cognition

In addition to the studies investigating the use of omega-3 fatty acids for the prevention of structural brain injury, omega-3s have been examined for their potential to improve neurocognitive functioning and psychological health. Preclinical studies have shown that diets low in omega-3s are associated with deficits in spatial learning and memory and impaired attention and performance.[44,45] However, findings of clinical studies are inconsistent. A meta-analysis of randomized control trials investigating the use of omega-3s for individuals diagnosed with Alzheimer's disease, cognitive impairment without dementia, and healthy controls found improvement in attention, processing speed, and immediate recall only for those with cognitive impairment without dementia.[37] Across these studies, omega-3 supplementation did not benefit healthy subjects or those diagnosed with Alzheimer's disease. A number of limitations in these studies preclude the ability to make any definitive conclusions from these results, including variation in the supplement dosage, treatment formulations, and the duration used among studies.[37] Other studies also found cognitive improvement for those considered to be deficient in omega-3s, but not in healthy subjects.[46,47]

While data described above suggest that service members with a low O3I may have deficits in neurocognitive performance compared to those with a high O3I,[36,48] randomized controlled trials investigating omega-3 supplementation have found no significant benefits on outcome measures in non-clinical populations.[48,49] A randomized controlled pilot study of 106 healthy active duty soldiers deployed in Iraq investigated the extent to which 2.5 grams per day of EPA and DHA (47% EPA, 38% DHA, and 4% DPA) for 60 days could enhance neurocognitive performance,

improve sleep quality, and decrease symptoms of depression and anxiety.[48] Despite demonstrating that supplementation of omega-3s is feasible in the deployed setting, the trial found no significant difference in neurocognitive or psychological health after omega-3 treatment. However, they did find that a decrease in self-reported daytime sleepiness was significantly associated with an increase in O3I. In another study, service members attending the Army Infantry Basic Officer Leaders Course (IBLOC) with the intention to complete the U.S. Army Ranger course (n=555) were enrolled in a randomized controlled trial to determine whether omega-3 supplementation could improve cognition and resilience to stress during intensive military training.[49] Cognitive assessment was completed at baseline, at week 14, and at week 16 following a 3-day combat simulation challenge. Dietary supplementation with 2.3 grams per day of EPA and DHA (2:1 ratio) for 24 weeks did not improve cognition or resilience. Notably, 310 service members did not complete the study due to withdrawal from the study, being lost to follow-up, dropping out of IBOLC or the Ranger course, or being considered no longer eligible, which could have contributed to these null results. Compliance to nutrition protocols may also have contributed to the null results, which is a common concern for observational studies that include nutrition protocols.[50]

Omega-3 Fatty Acids for Mild TBI Treatment and Recovery

Most clinical studies of omega-3 fatty acids have investigated their prophylactic use; however, some have begun to investigate the use of these fatty acids for treating post-concussive symptomology. Preclinical studies suggest that administering DHA during both the acute (1 day) and subacute (14 days) time frame following TBI may enhance cognitive recovery[51] and improve learning and memory.[52-55] Some preclinical studies have also suggested that the combination of exercise with a DHA-enriched diet may improve cognition following head injury.[11,56]

A limited number of clinical studies have explored the use of omega-3 fatty acids for treating mild TBI symptomology during both the acute (24–96 hours) and chronic (1 month or longer) time frame.[4,50] Some studies have reported faster mild TBI symptom resolution and return-to-play after omega-3 supplementation than after placebo treatment.[4] A recent study observed that supplementation with 2 grams of DHA daily for 12 weeks led to mild TBI symptom resolution an average of 4 days sooner and return-to-play approximately 5 days earlier than placebo treatment.[4,57] However, these results were observed in adolescent athletes, and most peer-reviewed studies of the effects of omega-3 supplementation on return-to-sport after mild TBI have only been completed in samples of individuals 18 years of age or younger. Further investigation in adults is needed given that recommended omega-3 intake levels vary by age.

Evidence on the durability of the positive effects of omega-3 supplementation is limited. One small, randomized control trial (n=38) evaluated the effects of a combined 3.5 grams DHA and EPA (a ratio of 2.4 grams DHA per 1.0 gram EPA) daily supplementation over the course of a football season (33 weeks) on serum biomarkers and found that while supplementation significantly increased both DHA and EPA plasma levels, it did not significantly affect serum NfL levels.[41] In addition, DHA concentrations returned to baseline values seven weeks after the end of treatment. It is important to note that symptoms were not reported in this study. Additionally, a 12-week randomized control trial (n=99) that consisted of a daily dose of 1,470 mg DHA and 147 mg EPA found no significant change in health-related quality of life after mild TBI.[58] Future studies should seek to correlate nutritional supplementation, biomarker data, and

clinical presentation to determine the extent to which omega-3 supplementation provides a clinical benefit to patients.

While current research findings neither refute nor fully support a clinical recommendation for omega-3 supplementation, surveys have shown that some sports medicine physicians do recommend omega-3 supplementation as a prophylactic treatment for athletes at high risk for mild TBI.[59,60] One qualitative survey indicated that sport dietitians and nutritionists may recommend omega-3 fish oil supplementation for concussion recovery without a clear rationale or protocol.[61] A survey of 257 sports medicine physicians revealed that 63 have prescribed omega-3 fatty acids for sports-related concussions, though only 39.7% of this group indicated that it was an effective treatment, and 57.1% indicated they were unsure of its effectiveness.[60] Service members with military occupational specialties that put them at risk for brain injury may also utilize omega-3 supplements at a higher rate than those in other MOS. In a study of 329 active duty military personnel, those classified as having a high risk of brain injury (breachers and shooting instructors; those with more deployments; those exposed to more blast overpressures and explosions; those who reported more TBIs, brain fog, and headaches) had the highest intake of omega-3 supplements and foods high in omega-3s.[18] While these studies demonstrate individual choices to use omega-3 supplements, the current *VA/DOD Clinical Practice Guideline for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury* only broadly cites nutrition as a potential modifier of the physiological response to mild TBI,[62] and there is no specific nutritional intervention currently cited in clinical practice guidelines for the treatment of mild TBI. The level of evidence on omega-3 supplementation to date does not support a change to existing VA/DOD mild TBI clinical recommendations.

Omega-3 Fatty Acid Dosage and Dietary Intake Recommendations

In the U.S, the recommended daily intake of different nutrients varies by age, sex, and available scientific evidence.[63] Strong evidence leads to a Recommended Dietary Allowance for a nutrient, while an Adequate Intake (AI) level is established when evidence is not sufficient to develop an RDA.[64] Based on current evidence, the daily intake of omega-3s for general health of those over age 18 is determined using an AI level: 1.6 grams per day for men and 1.1 grams per day for women.[65] For healthy individuals, consuming up to 5 grams total of DHA and EPA daily is generally considered safe by the FDA[65,66] and other worldwide governing bodies such as the European Food Safety Authority.[67]

However, the Centers for Disease Control and Prevention estimates that up to 80% of the U.S. population is deficient in omega-3s.[68] Evidence suggests that both healthy and injured individuals fall short of the daily AI level for omega-3 fatty acids. Furthermore, consuming the optimal AI level is a particular concern for warfighters who may operate in environments with limited access to foods rich in omega-3 fatty acids.[48]

While AI levels have been established for healthy individuals, the dosage of omega-3 supplementation examined across the TBI literature varies widely, and currently there is no generally accepted recommended intake level for mild TBI patients. Most research on omega-3 supplementation following TBI has been completed in preclinical models, and the findings may not directly translate to humans as TBI models may not replicate the complexities of human TBI pathology.[51] Preclinical models also allow researchers to maintain consistent diets for the

subjects, whereas human diets are harder to control. Some studies have investigated whether there is a dose-response relationship between omega-3 supplementation and outcomes related to TBI.[69,70] A recent preclinical study compared the levels of glial fibrillary acidic protein and CD68—biomarkers for astrocyte activation and microglial activity, respectively—in mice that received either a high dose (250 mg DHA and 125 mg EPA) or low dose (50 mg DHA and 25 mg EPA) of omega-3s for 30 days prior to sustaining a mild TBI.[69] The results showed that high dose omega-3 supplementation before injury resulted in a lower concentration of GFAP following head injury than both low dose omega-3 preinjury supplementation and no preinjury supplementation. Similar trends were observed for CD68 levels. Other preclinical studies have also found that a high dose of omega-3 fatty acids, which is equivalent to 10 grams of DHA and EPA in humans, improves neurological, cognitive, and molecular outcomes following mild TBI.[70]

In humans, some studies have shown a dose-response relationship between the amount of omega-3s prescribed and the resulting O3I, which may help support efforts to determine the optimal dose. In an observational study (n=69) analyzing the response to different doses of DHA supplementation in healthy athletes, researchers observed significant increases in O3Is for groups supplementing with 2 grams, 4 grams, and 6 grams of DHA.[21] Across treatment groups, those taking 6 grams of DHA reached the target of a O3I of at least 8% eight weeks after supplementation began whereas those taking 2 grams or 4 grams did not meet this benchmark until later in the season. Additionally, the treatment group receiving 6 grams sustained a O3I of at least 8% at Week 8 of supplementation until the end of the 27-week study. However, there was no statistically significant difference in O3Is between those who received 2 grams and those who received 4 grams of DHA over the course of the study. A recent narrative review provides a theoretical framework for those at high risk of mild TBI to consider a variety of supplements, including a daily dose of 2 grams to 4 grams of omega-3s, of which 2 grams is DHA, as both a preventative measure and post-injury regimen; importantly, the article indicates a thorough baseline health assessment be included to understand individual differences.[20] Together, these studies suggest that there is some evidence that supplementation with 2 grams or more of omega-3 fatty acids can increase the O3I and that higher doses may be needed to reach optimal blood saturation. The International Olympic Committee currently recommends about 2 grams per day of omega-3 fatty acid supplements for high performance athletes.[71]

While promising for determining blood saturation point benchmarks, the extent to which higher doses of omega-3 supplements correlate to the alleviation of mild TBI symptoms is unknown. Well-designed randomized controlled trials are warranted to further investigate the effectiveness of these dose regimens in humans as there is inconsistency in the omega-3 dosage used across clinical studies. Efforts to control for dietary intake during the study duration should be incorporated into study protocols and monitored for compliance, such as educating participants on foods to avoid that are high in omega-3 fatty acids and administering dietary assessment questionnaires.[21,31,49] The bioavailability of DHA and EPA also varies by body weight;[72] therefore, tailoring the omega-3 dosage may be necessary to address the variability in patients' baseline nutrient intake and diet.[20]

Contraindications and Adverse Events

Generally, omega-3 intake is considered safe up to 5 grams per day when consumed through both dietary intake and supplements.[66] Most interventional studies providing omega-3 supplements report good tolerability,[73] though some adverse effects have been reported including gastrointestinal distress, eructation, halitosis, and acne.[3] No serious adverse events have been reported in clinical studies. Many studies do not elaborate on reasons for noncompliance; however, some report pill burden, forgetting to take pills, difficulty swallowing, and aversion to the taste as reasons for not following omega-3 supplementation protocols.[74] The use of masking agents may address poor taste, the most frequently reported reason for noncompliance.[57,73,74]

EPA is known to disrupt platelet aggregation, which has raised concerns of an increased risk of bleeding as a result of omega-3 supplementation,[75,76] particularly in patients taking anticoagulant medications.[77,78] However, a recent systematic review and meta-analysis on randomized controlled trials (n=11 studies; 120,643 subjects total) found that while there may be an increased risk of bleeding (0.6%) in response to an increased daily dose of EPA, clinical evidence to date does not suggest an increased risk of intracranial bleeding or hemorrhagic stroke with omega-3 supplementation.[79] Notably, the average age of patients across these studies was 75 years, which limits the generalization of these findings to younger patients who reflect the average age of military service members. No clinical research to date has been published to confirm whether this risk is observed in patients with mild TBI. Omega-3s may interact with and enhance the effects of anticoagulant medications, so patients concomitantly taking omega-3 supplements and anticoagulant medication should be carefully monitored.[80]

CONCLUSIONS & IMPACT TO THE WARFIGHTER

- Although an O3I of at least 8% is considered optimal for protection from cardiovascular events, an optimal O3I for TBI is unknown. Up to 80% of the U.S. population is estimated to be deficient in omega-3s.
- Omega-3 fatty acids may help mitigate the secondary physiological injury cascade that occurs after mild TBI, and supplementation may shorten recovery time, but data are inconclusive.
- Most clinical studies have not investigated the durability of benefits from omega-3 supplementation, though a single study suggested that benefits may last up to seven weeks post-treatment.
- There is currently no strong evidence that omega-3 dietary supplementation results in a bleeding disorder; however, no studies of TBI patients directly investigating this risk have been reported.
- For healthy individuals, up to 5 grams of DHA and EPA per day is generally considered safe per the FDA, but how this recommendation should change for those at risk for mild TBI – such as warfighters in high risk occupational specialties – is currently unknown.
- To address the variability between patients' baseline nutrient intake, diet, body mass, physical activity, and current medical conditions, an objective baseline assessment of a

patient's omega-3 index prior to recommending omega-3 supplements for prevention or treatment of mild TBI may support individual tailoring of omega-3 dosages.

- Noncompliance with omega-3 supplementation protocols is a considerable concern and may explain the inconsistent results among clinical nutrition studies. In some clinical trials, compliance with nutrition protocols appears to decrease as symptoms improve.[57]

- While some studies have correlated low omega-3 status to deficits in cognitive performance, it is unclear whether additional omega-3 supplementation can optimize cognitive performance in healthy individuals with no history of mild TBI.

- The current VA/DOD mild TBI clinical recommendations do not specify any nutritional intervention for the treatment of mild TBI, and the level of evidence on omega-3 fatty acid supplementation to date does not support a change to those recommendations.

- Future well-designed randomized controlled studies are needed to investigate the neuroprotective role of omega-3 fatty acids as a method to minimize secondary injury following mild TBI in humans.

Prepared by:

Traumatic Brain Injury Center of Excellence
Clinical Translation Office
dha.ncr.TBICoEResearch@health.mil

DISCLAIMER

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