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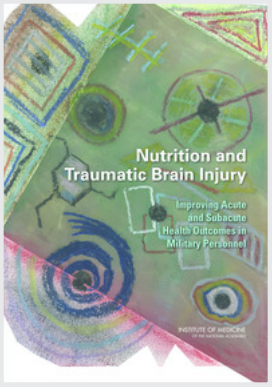

Nutrition and Traumatic Brain Injury: Improving Acute and Subacute Health Outcomes in Military Personnel (2011)

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Summary

The U.S. military has seen significant advances in the prevention and treatment of wartime injuries. Science, medicine, and engineering have progressed to the point that the number of casualties of current wars is at a historic low compared with the wars of the past century. Today's warfighters benefit from multiple protections against penetrating injury. However, more widespread use of weapons like improvised explosive devices (IEDs) is leading to a higher number of nonpenetrating head and neck wounds, particularly traumatic brain injury (TBI). Mild single and recurrent injuries are especially worrisome because they might be silent—and consequently not treated—for months or years, only later becoming symptomatic and jeopardizing optimal health and performance. Although estimates of incidence vary, TBI has emerged as an important concern for the military, which in 1992 established the Department of Defense (DoD)/Department of Veterans Affairs (VA) Defense and Veterans Brain Injury Center to serve the military through clinical care, research initiatives, and educational programs.

Any injury to the brain, the main center for receiving and processing information and response, will likely result in a complex disease or condition. The military defines TBI as a traumatically induced structural injury or physiological disruption of brain function resulting from an external force that is indicated by new onset or worsening of symptoms involving level of consciousness, memory, mental or neurological states, or intracranial lesion (DOD, 2009). TBI has also been categorized as an ongoing process that affects multiple organs and systems and that may cause or accelerate other diseases and disorders that can reduce life expectancy (Masel and DeWitt, 2010). Although the characteristics of the disease will vary with the individual and injury and the sequence of events is not yet completely understood, there are several common pathobiological processes, including intracranial hemorrhage, excitotoxicity, ionic disturbances, decreased cerebral blood flow, edema, oxidative stress, inflammation, and damage and death of brain cells that occur during the acute (i.e., within minutes) and subacute (i.e., within 24 hours) phases. Other effects will manifest

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much later after the injury, although they will still be a consequence of the initial insult. In this longer-term phase, TBI has been associated with neurological disorders, neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease, and chronic traumatic encephalopathy), neuroendocrine disorders, psychiatric and psychological diseases, nonneurological disorders, and musculoskeletal dysfunction. Managing this multifaceted disease is a challenge. Given TBI's complex pathobiology and acute, subacute, and long-term effects, both the timing and duration of administration of any potential interventions are important to consider.

Nutrition has emerged as a possible approach for the prevention of or therapy for injuries to the brain, including neurodegenerative disorders and ischemia. DoD requested that the Institute of Medicine (IOM) convene an ad hoc committee to review the existing evidence for the potential role of nutrition in providing resilience or treating the acute and subacute effects of neurotrauma, with a focus on TBI.

SCOPE OF THE STUDY AND APPROACH OF THE COMMITTEE

This report reviews nutritional approaches that show promise in providing resilience or treating the acute and subacute effects of TBI. The committee was not asked to evaluate the role of nutritional therapies in the rehabilitation phase or the potential role of nutrition in ameliorating long-term effects of TBI. It is important to note that the chronological boundaries of acute, subacute, and long-term effects are not clear. For example, an event such as angiogenesis, which is typically associated with long-term wound healing, is initiated within the brain during the acute phase. This report therefore includes some studies that also evaluate seemingly long-term outcomes that may be initiated in the acute and subacute phases of the disease. This report does not address other outcomes such as neurodegenerative (e.g., Alzheimer's disease, Parkinson's disease), neuroendocrine, psychiatric, and other nonneurological disorders that appear later in life and may be associated with TBI but for which a causal relationship with the original injury has not been clearly established.

In spring of 2010, the IOM appointed a committee of 11 experts with extensive knowledge in the areas of neurology; nutritional sciences, clinical nutrition, and dietetics; physiology; physical medicine and rehabilitation; psychiatry and behavioral science; biochemical and molecular neuroscience; epidemiology/methodology; and the pathobiology of TBI. Two public workshops featuring presentations by civilian and military subject matter experts in TBI provided important information for the committee. A review of the scientific literature was conducted to examine physiological sequelae and metabolic responses to TBI, with the purpose of identifying mechanistic interventions. Nutrients were reviewed for their efficacy on TBI or on brain injuries with pathologies related to TBI, such as hypoxia, epilepsy, and subarachnoid hemorrhage. The committee also reviewed current practice guidelines for specific nutritional approaches to the clinical treatment of TBI on the battlefield, in garrison, or in hospital intensive care units (ICUs). In general, the nutrients were selected based on their potential role in restoring cellular energetics, reducing oxidative stress and inflammation, and repairing and recovering from the injury. The following nutritional interventions were identified for review: energy needs for severe cases of TBI, acetyl coA, antioxidants, branched-chain amino acids, choline, creatine, ketogenic diets, magnesium, nicotinamide adenine dinucleotide (NAD^+), n-3 fatty acids, polyphenols, probiotics, vitamin D, and zinc. Three of the nutritional interventions (i.e., acetyl-L-carnitine, niacin, and probiotics) initially selected were not included in the report because of insufficient evidence to reach conclusions about effectiveness from animal and human studies, or concerns for harm.

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CONCLUSIONS AND RECOMMENDATIONS

This report emphasizes the importance of nutrition not only to augment overall defensive mechanisms against the effects of TBI but also as postinjury treatment to lessen the acute and subacute effects of TBI. The committee found that the majority of clinical guidelines for TBI do not specifically address optimal nutritional support for TBI. Based on the literature searches the committee concluded that conducting a review of the nutrition approaches to improve long-term effects of TBI, which was part of the initial task and later excluded because of financial constraints, would also be important (see also workshop papers by Metzger, Gomez-Pinilla, and Sands in Appendix C).

The recommendations were reached by consensus and are a reflection of the gap in data about the efficacy of most of the nutrition approaches reviewed. For this reason, except for early feeding of severe cases, the committee thought it premature to direct DoD to adopt any of them at this time. For the approaches that are supported by enough preclinical and, in some cases, clinical data, the committee sees the potential benefits for TBI patients and reached consensus about research needed in some promising areas. The report includes recommendations for research on the specific nutrition approaches that are promising and warrant further investigation. The research recommended will serve to confirm published results and to refine the protocols (i.e., optimal route of administration, timing, and dose).

The committee made recommendations for updating the evidence-based guidance for severe TBI with the provision of early feeding (Box S-1) as well as for research on continuing the development of animal models and the identification of biomarkers (Box S-2), on assessing nutritional status and intake of military populations (Box S-3), and on promising areas of nutrition research (Boxes S-4 and S-5). Finally, the committee includes a general recommendation to develop and update evidence-based guidance for TBI in the future, as more evidence about the value of nutritional interventions becomes available (Box S-6). The committee offers here its reflections on the prioritization of research based on its opinion of the likelihood of positive results for lessening the effects of TBI. Research on interventions for which human trials to explore the efficacy of improving the outcomes of TBI already exist or are ongoing have been presented as "most promising research" (Box 17-4). Research on interventions for which animal studies in TBI or human studies in associated conditions have shown improvements in outcomes are presented as "other research" (Box 17-5). DoD is encouraged to conduct the research internally, to support extramural research, or to collaborate with others in order to obtain answers more effectively.

The committee recognizes that conducting clinical research on TBI is extremely complex and that the understanding of the differences in pathophysiology between mild and severe

BOX S-1
Standardize the Provision of Energy and Protein to Patients with Severe TBI

RECOMMENDATION 6-1. The committee recommends that evidence-based guidelines include the provision of early (within 24 hours after injury) nutrition (more than 50 percent of total energy expenditure and 1–1.5 g/kg protein) for the first two weeks after injury. This intervention is critical to limit the intensity of the inflammatory response due to TBI, and to improve outcome.

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BOX S-2
Continue Improving Animal Models and Identifying Biomarkers

RECOMMENDATION 3-1. The committee recommends that DoD, in cooperation with others, refine the existing animal models to investigate the potential benefits of nutrition throughout the spectrum of TBI injuries, that is, mild/concussion, moderate, severe, and penetrating, as well as repetitive and blast injuries. Development of animal models is particularly urgent for concussion/mild TBI and brain injuries due to blast as well as for repetitive injuries. These models also will aid in understanding the pathobiology of TBI, which is particularly needed for concussion/mild TBI, blast, and repetitive injuries.

RECOMMENDATION 3-2. The committee recommends that DoD, in cooperation with others, continue to develop better clinical biomarkers of TBI (i.e., mild/concussive, moderate, severe, penetrating, repetitive, and blast injuries) for the purposes of diagnosis, treatment, and outcome assessment. In addition, the committee recommends the identification of biomarkers specifically related to proposed mechanisms of action for individual nutritional interventions.

injuries is continuously evolving. Randomized clinical trials in a TBI population are difficult to carry out, and long-term prospective studies among high-risk populations are costly. Still, the committee emphasizes the need to follow best practices when designing such studies, and the importance of the following: (1) using appropriate biomarkers and animal models (see recommendations 3-1 and 3-2), (2) considering the full spectrum of TBI, (3) recording adverse effects, (4) recording gender and age differences, (5) carefully monitoring the quality of the compounds being tested, (6) using effective chemical forms and sources, based on their bioavailability, metabolism, and ability to reach the target area, (7) optimizing the route and timing of administration and dosage, and (8) recording synergistic and antagonistic effects with nutrients and dietary supplements or other substances in the diets of military personnel.

Energy and Protein Needs in Patients with Severe TBI

The current clinical practice guidelines for patients with TBI or other critical illnesses recommend early feeding, but the elements of the feeding regimen vary substantially, from

BOX S-3
Assessing Nutrition Status

RECOMMENDATION 5-1. DoD should conduct dietary intake assessments in different military settings (e.g., when eating in military dining facilities or when subsisting on a predominantly ration-based diet) both predeployment and during deployment to determine the nutritional status of soldiers as a basis for recommending increases in intake of specific nutrients that may provide resilience to TBI.

RECOMMENDATION 5-2. Routine dietary intake assessments of TBI patients in medical treatment facilities should be undertaken as soon after hospitalization as possible to estimate preinjury nutrition status as well as to provide optimal nutritional intake throughout the various stages of treatment.

RECOMMENDATION 5-3. In individuals with TBI, DoD should estimate pre-injury and post-injury dietary intake or status for those nutrients, dietary supplements, and diets that might show a relationship to TBI outcome. For example, based on the current evidence, the committee recommends collecting those estimates for creatine, n-3 fatty acids, choline, and vitamin D. The data could be used to investigate potential relationships between preinjury nutritional intake or status and recovery progress. Such data also would show possible synergistic effects between nutrients and dietary supplements.

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BOX S-4
Most Promising Research Recommendations

RECOMMENDATION 6-2. DoD should conduct human trials to determine appropriate levels of blood glucose following TBI to minimize morbidity and mortality. These should be clinical trials of early feeding using intense insulin therapy to maintain blood glucose concentrations at less than 150–160 mg/dL versus current usual care of acute TBI in ICU settings for the first two weeks.

RECOMMENDATION 6-3. DoD should conduct clinical trials of the benefits of insulin therapy for care of acute TBI in inpatient settings with total parenteral nutrition (TPN) alone (or plus enteral feeding) versus enteral feeding alone. The goals for blood glucose in the TPN group should be lower (e.g., less than 120 mg/dL) than in the enteral group (e.g., less than 150–160 mg/dL). Variables to measure include clinical outcomes and incidence of hypoglycemia.

RECOMMENDATION 6-4. DoD should conduct studies to determine the optimal goals for nutrition (e.g., when to begin meeting total energy expenditure for optimal lean tissue maintenance or repletion) after the first two weeks following severe injury.

RECOMMENDATION 8-1. DoD should continue to monitor the literature on the effects of nutrients, dietary supplements, and diets on TBI, particularly those reviewed in this report but also others that may emerge as potentially effective in the future. For example, although the evidence was not sufficiently compelling to recommend that research be conducted on BCAAs, DoD should monitor the scientific literature for relevant research.

RECOMMENDATION 9-1. DoD should monitor the results of the Citicoline Brain Injury Treatment (COBRIT) trial, a human experimental trial examining the effect of CDP-choline and genomic factors on cognition and functional measures in severe, moderate, and complicated mild TBI. If the results of that trial are positive, DoD should conduct animal studies to define the optimal clinical dose and duration of treatment for choline (CDP-choline) following TBI, as well as to explore choline's potential to promote resilience to TBI when used as a preinjury supplement.

RECOMMENDATION 10-1. Based on the evidence supporting the effects of creatine on brain function and behavior after brain injury in children and adolescents, DoD should initiate studies in adults to assess the value of creatine for treating TBI patients.

RECOMMENDATION 13-1. DoD should conduct animal studies that examine the effectiveness of preinjury and postinjury oral administration of current commercial preparations of purified n-3 fatty acids on TBI outcomes.

RECOMMENDATION 13-2. Based on the evidence that fish oil decreases inflammation within hours of continuous administration, human clinical trials that investigate fish oil or purified n-3 fatty acids as a treatment for TBI are recommended. For acute cases of TBI, it should be noted that there are intravenous fish oil formulations available in Europe, but these are not approved by the FDA. Continuous enteral feeding with a feeding formula containing fish oil should provide equivalent effects for this purpose in the early phase of severe TBI when enteral access becomes available.

RECOMMENDATION 16-1. Based on a report showing efficacy in humans, the committee recommends that animal studies be conducted to determine the best practices for zinc administration after concussion/mild, moderate, and severe TBI, such as determining the therapeutic window for zinc administration, the length of treatment time for greatest efficacy, and the optimal level of zinc to improve outcomes. These trials should also evaluate the safety of zinc, based on concerns about toxicity and overload. Results from these studies should be used to design human clinical trials using zinc as a treatment for TBI.

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BOX S-5
Other Research Recommendations

RECOMMENDATION 7-1. Based on the literature from animal and human trials concerning stroke and epilepsy, DoD should consider a clinical trial with TBI patients using an array of antioxidants in combination (e.g., vitamins E and C, selenium, beta-carotene) should be considered by DoD.

RECOMMENDATION 11-1. DoD should conduct animal studies to examine the specific effects of ketogenic diets, other modified diets (e.g., structured lipids, low-glycemic-index carbohydrates, fructose), or precursors of ketone bodies that affect energetics and have potential value against TBI. These animal studies should specifically consider dose, time, and clinical correlates with injury as variables. Results from these studies should be used to design human studies with these various diets to determine if they improve outcome against severe TBI. These studies should include time as a variable to determine whether there is an optimal initiation point and length of use.

RECOMMENDATION 11-2. If these studies show benefits, DoD should further investigate whether the potential beneficial effect of such ketogenic or modified diets or precursors to ketone bodies applies to concussion/mild and moderate TBI. Before conducting these studies, DoD should consider the feasibility (i.e., how to ensure compliance with a modified diet) of using diets that affect the metabolic energy available, such as ketogenic diets, for the treatment of TBI.

RECOMMENDATION 14-1. Based on positive outcomes in small-animal models of TBI with curcumin and resveratrol, DoD should consider conducting human trials. In addition, other flavonoids (e.g., isoflavones, flavanols, epicatechin, theanine) should be evaluated in animal models of TBI.

RECOMMENDATION 15-1. The committee recommends more animal studies be conducted to determine if vitamin D enhances the beneficial actions of progesterone in the treatment of TBI. If this synergistic effect is confirmed in animals, then studies in humans should be conducted to evaluate the extent to which vitamin D supplementation might improve the efficacy of progesterone treatment.

RECOMMENDATION 15-2. Based on animal studies showing a requirement of vitamin D for the efficacy of progesterone therapy, future animal studies are recommended to test the efficacy of using vitamin D supplements to improve resilience to TBI. Should the data from animal studies support use of this steroid hormone, human trials should be implemented to test the efficacy of vitamin D in populations at high risk for TBI.

RECOMMENDATION 16-2. Future work is needed in both humans and animal models to determine the extent to which chronic preinjury zinc supplementation can improve resilience in the event of a TBI.

the route of administration to the specific timing of initiation and the optimal method to estimate energy needs.

Based on recent meta-analyses showing that mortality and morbidity of TBI patients are improved by early feeding, the committee strongly supports the provision of energy and protein to patients with severe TBI early after injury. This important recommendation should

BOX S-6
Future Update of Evidence-Based Guidelines

RECOMMENDATION 2-1. Evidence-based nutrition guidelines specific for severe TBI should be updated. These guidelines should address unique nutritional concerns of severe TBI when different from generic critical illness nutrition guidelines (e.g., meeting energy needs and benefits of specific nutrients, food components, or diets). In addition, current guidelines to manage mild and moderate TBI should include recommendations for nutritional interventions. The guidelines should be developed in a collaborative manner with the various key stakeholders (e.g., American Dietetic Association, Department of Veterans Affairs, DoD).

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be implemented immediately and will achieve significant positive outcomes by reducing the inflammatory response, which is likely to be at its height during the first 2 weeks after the injury.

Continue Improving Animal Models and Identifying Biomarkers

Appropriate animal study designs and biomarkers of injury and recovery are important components of a research agenda to support any hypothesis about the benefits of nutrition interventions (Box S-2). Reviews of the literature on animal models reveal limitations, especially for animal models of mild/concussion and blast TBI. Likewise, recent reviews on biomarkers for TBI reveal substantial limitations that decrease their value, such as poor discrimination between levels of injury severity, especially mild TBI; limited sensitivity; poor correlation between serum and brain levels; or systemic increases in the absence of TBI. Developing better clinical biomarkers of all types of TBI for the purposes of diagnosis, treatment, and outcome assessment is warranted. Nutrient mechanisms of action in TBI are still being studied, and it would be premature to identify any marker of nutritional interventions. Multiple biomarkers in conjunction with clinical data may offer better predictability of outcome.

Conducting Nutrition Assessments

Conducting nutrition assessments among active duty military personnel is costly and logistically challenging, particularly in combat zones, but collecting such information is necessary because the equivalent of NHANES data (i.e., health and nutritional data for adults and children in the United States) is lacking for the military population. Data on food consumption and nutrient intakes prior to mobilization would be valuable when making nutrition recommendations as a preventive approach. Knowing the nutrition status of TBI patients pre- and postinjury will also be essential to determine whether specific nutrient supplements would improve their health outcomes. The committee makes general recommendations about evaluating nutrition status in the military (Box S-3).

Research Needs on Nutritional Goals for Severe TBI

Although the importance of early feeding for patients with severe TBI is recognized and recommended in this report, there are still key questions, such as determining the optimal blood glucose concentration for the period immediately after a severe injury. The committee concluded that it is important to develop best feeding practices both for the initial period after TBI when the systemic inflammatory response is likely to be at its height, and also after about two weeks when concern about lean tissue maintenance and repletion assumes greater importance and tolerance to feeding is likely to be improved. Both hyperglycemia and hypoglycemia can occur in the critically ill, with the risk of hypoglycemia being higher in brain tissues that have glucose as their required source of energy. A number of recent studies have shown the negative effects of hypoglycemia on the likelihood of mortality in the critically ill, including TBI patients. The concept of permissive underfeeding has been applied to TBI patients in order to reduce the risk of hyperglycemia and its adverse effects. Increasing protein intake while following a lower energy intake regimen will improve the retention of lean tissue and may favorably affect clinical outcome in these patients. Intensive insulin therapy has been widely used to produce normal blood glucose levels, but its use appears most valid for the reduction of inflammation and improvement in morbidity and mortality in surgical patients. The utility of intensive insulin therapy has not been established

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in medical patients, and although a few human studies have been conducted with intensive insulin therapy in TBI patients, the goals for the level of nutritional support and glucose homeostasis still need to be established (Box S-4).

Research Needs on Nutrients and Dietary Supplements

The existing evidence varies, but not enough has been accumulated on any of the selected nutritional interventions to recommend their provision to increase resilience or ameliorate the acute effects of TBI. For some of the selected interventions, studies have demonstrated benefits in animal models of TBI or related brain injuries, but there are no clinical trials that confirm similar beneficial effects in humans. In other cases, human trials are under way, and the military should review those studies as the results are made public. Depending on the strength of the evidence for resilience or treatment, the committee makes recommendations for research in animal models or humans to confirm efficacy or determine the optimal dose, route of administration, or timing of administration.

Antioxidants

Oxidative stress is identified early after the initial injury, and compounds that intercept the production of reactive oxygen species could be beneficial for TBI outcomes. However, based on the fact that, even in the case of the most-studied compounds such as vitamins C and E, the use of single antioxidants has not been successful in treating oxidative-related diseases, the committee does not recommend any future research with single antioxidants and TBI. The committee's recommendation for further research is based on the limited success of some combinations of antioxidants in treating stroke and cancer.

Branched-Chain Amino Acids

Branched-chain amino acids (BCAAs) are commonly used by military personnel seeking a good source of protein to build muscle mass and reduce fatigue. Although these performance claims for BCAAs are not well supported, the possibility that BCAAs will help TBI patients cannot be discarded. BCAAs are precursors of neurotransmitters and compete with other neurotransmitters for transport through the blood-brain barrier. However, there is no strong evidence from animal or human studies on its effects in brain injury, and the committee suggests that research on BCAAs and TBI should not be a priority for the military until more compelling evidence is collected by other researchers.

Choline

Choline has been shown to act as an anti-inflammatory and antioxidant in other diseases, and also to decrease calcium-mediated cell death, a feature of TBI. Although substantial research has been conducted on choline and treatment of brain injury (stroke), differences in study design and study limitations have produced varying results; no conclusions about its efficacy can therefore be made at this time. There is one ongoing human trial on the effect of CDP-choline on cognition and functional measures on severe, moderate, and complicated mild TBI being led by a member of the committee. The committee recognizes the importance of this trial in that the findings will reveal more insights about the potential for this nutrient and whether there is a need for more human studies.

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Creatine

Military personnel are using creatine in the form of dietary supplements to increase strength and muscle mass. In the context of TBI, the committee found good evidence of improvements in cognition and behavior from trials with creatine in children and adolescents. Although this evidence comes from long-term studies, treatment with creatine was started early after injury and may have influenced disease processes during the acute phase. In fact, creatine is thought to maintain mitochondrial energetics and improve cerebral vascular function, both of which are disrupted during the acute phase of TBI. The military is urged to resolve questions about whether these results can be extrapolated to adults and about the timing of administration and optimal dose.

Ketogenic Diet

Results from studies of children with epilepsy suggest that ketogenic diets (or other modified diets that increase levels of ketone bodies) might be therapeutic for TBI. It is hypothesized that ketogenic diets might provide an alternative source of energy and reduce dependence on glucose, whose metabolism is impaired after TBI. There are, however, concerns about the feasibility of these diets in the TBI context, where meeting nutritional needs is important, especially early after injury; adherence to ketogenic diets by patients might also be difficult once they are outside a hospital setting.

Magnesium

Magnesium has a role in inhibiting the actions of the excitatory neurotransmitter glutamate by regulating calcium entry into the postsynaptic neuron, a process intimately related to a TBI event. Despite this seemingly neuroprotective action, there is no clear evidence that magnesium supplementation will affect TBI outcomes. The committee offered no recommendation for supplementing with or conducting further research on magnesium. The window of opportunity for magnesium use in the treatment of TBI is a critical issue that remains to be addressed. The military should follow the results from current magnesium trials, which will evaluate potential benefits of magnesium when administered one to two hours after the onset of brain damage.

N-3 Fatty Acids

Despite surveys indicating that n-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) are being taken as dietary supplements by military personnel, it has been suggested that the n-3 fatty acid status of the active duty military population might be low. Because it is well documented that fish oil supplementation decreases inflammation, n-3 fatty acids are the subject of many studies evaluating their health benefits and elucidating their mechanism of action. The ratio of n-3:n-6 composition may affect cell membrane fluidity, thickness, or other characteristics. Although animal models and human studies on other brain injuries suggest they may provide benefits, there has been no human trial evaluating the effects of n-3 fatty acids on resilience to or treatment of TBI.

Polyphenols

Polyphenols are a heterogeneous group of compounds widely found in nature that have been evaluated for their benefits to health when consumed either singly or in combination,

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and as either dietary supplements or as a component of foods. The committee selected flavonoids as a group of compounds, and curcumin (a flavonoid) and resveratrol (a stilbene) as single components. Although none of these compounds has been tested in human trials, the positive findings from animal models of TBI indicate that resveratrol and curcumin warrant more research to study their effects both in providing resilience to and in treatment of TBI.

Vitamin D

The role of vitamin D in the brain has only recently been recognized and is not well understood. Vitamin D and its receptor are thought to act by binding to DNA response elements that regulate gene transcription involved in cell proliferation, differentiation, and neural function in the brain.

Trials to evaluate the effects of progesterone in animal models of TBI have revealed that adequate vitamin D status might affect the outcomes of progesterone treatment, an example of the synergistic effects that may result from interactions among compounds. Vitamin D's potential to increase resilience to TBI is supported by findings that vitamin D alone was also neuroprotective against animal models of stroke. Although there are only a few studies on vitamin D's benefits for TBI treatment, the findings are promising and need to be evaluated further.

Zinc

Zinc is an essential nutrient required for the function of many enzymes in the central nervous system. In the brain, zinc is released in the synaptic cleft where it modulates the activity of neuroreceptors. An excessive release of zinc can result in neural cell death. In the context of TBI, zinc deficiency might exacerbate the oxidative cascade that results in cell death. The nutrition assessments of TBI patients recommended here will help substantiate the hypothesis that zinc deficiency affects outcomes of TBI. Findings from animal studies suggest that supplementation of diets beyond required levels might be even more beneficial, and this possibility should be explored. Trials of patients with severe closed head injuries showed positive effects after treatment with zinc.

FUTURE APPLICATION OF RESEARCH TO CLINICAL CARE

Ultimately, interventions for which there is sufficient evidence of efficacy need to be transferred to clinical care situations. In general, the majority of clinical guidelines for critical care and for TBI do not include specific recommendations to ensure adequate nutrition early after injury or in the long term. The findings of the research gaps outlined above would present an opportunity to update the existing clinical guidelines with evidence-based nutritional interventions.

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