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Functional Medicine Approach to Traumatic Brain Injury

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ABSTRACT

Background: The U.S. military has seen dramatic increases in traumatic brain injuries (TBIs) among military personnel due to the nature of modern-day conflicts. Conventional TBI treatment for secondary brain injuries has suboptimal success rates, and patients, families, and healthcare professionals are increasingly turning to alternative medicine treatments.

Objective: Effective treatments for the secondary injury cascades that occur after an initial brain trauma are unclear at this time. The goal of successful treatment options for secondary TBI injuries is to reduce oxidative stress, excitotoxicity, and inflammation while supporting mitochondrial functions and repair of membranes, synapses, and axons.

Intervention: A new paradigm of medical care, known as functional medicine, is increasing in popularity and acceptance. Functional medicine combines conventional treatment methods with complementary, genetic, holistic, and nutritional therapies. The approach is to assess the patient as a whole person, taking into account the interconnectedness of the body and its unique reaction to disease, injury, and illness while working to restore balance and optimal health. Functional medicine treatment recommendations often include the use of acupuncture, Ayurveda, chiropractic manipulation, detoxification programs, herbal and homeopathic supplements, specialized diets, massage, meditation and mindfulness practices, neurobiofeedback, nutritional supplements, *t'ai chi*, and yoga. At present, some of these alternative treatments appear to be beneficial, but more research is needed to validate reported outcomes.

Conclusions: Few clinical studies validate the effectiveness of alternative therapies for TBIs. However, further clinical trials and empirical studies warrant further investigation based on some reported positive results from research studies, case histories, anecdotal evidence, and widespread popularity of some approaches. To date, only nutritional therapies and hyperbaric oxygen therapy have shown the most promise and potential for improved outcomes for the treatment of secondary TBI injuries.

Keywords: functional medicine, traumatic brain injury, omega-3 fatty acids, dietary supplements, hyperbaric oxygen therapy, alternative medicine

INTRODUCTION

The U.S. military has seen a dramatic increase in traumatic brain injuries (TBIs) among military personnel during conflicts in recent years. According to estimates by the Department of Defense (DoD) and the Defense and Veteran's Brain Injury Center, the majority of military TBIs are sustained during motor vehicle accidents, gunshot wounds, blasts, or a combination of these. An estimated 22% of all combat casualties are thought to be caused directly by TBIs.[1] Compared to civilian populations, veterans are disabled for longer periods of time with symptoms of cognitive and behavioral impairments. Veterans frequently experience additional symptoms of post-traumatic stress disorder (PTSD) and chronic pain, and are at increased risk for suicide and substance abuse.

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When the brain is injured, brain metabolism is altered and neurons are highly susceptible to damage from free radicals and mitochondrial dysfunction. Thus begins a pathologic process that can sometimes take years to repair. Conventional TBI treatment for these secondary brain injuries has had suboptimal success rates. Because of this, TBI victims, their families, and some healthcare professionals are increasingly exploring new treatment options that are perceived to be less injurious to health, more beneficial, and sometimes their only hope. As Joel Goldstein—whose son sustained a severe TBI in an automobile accident—the founder of the Bart Foundation, and author of *No Stone Unturned: A Father's Memoir of His Son's Encounter with Traumatic Brain Injury*—states: ''Unconventional therapies are not merely a reasonable option, they are a necessity.''[2] These ''new'' treatments include cell-based, genetic, holistic, integrative, nutritional, and hyperbaric oxygen therapies. Emerging treatment options for the treatment of secondary brain injuries is the focus of this article.

A literature review of alternative treatment options for patients with TBI was completed for this article with a focus on research reported between the years 1980 and 2017. Search criteria included TBI in the military; alternative and functional medicine therapies for brain injury; blogs and foundations for patients with TBI; and supplements, nutrition, and alternative therapies for the treatment of TBI. Because there are few clinical studies validating the effectiveness of alternative treatments for TBIs to date, promising therapies were selected for discussion based on reported objective evidence found in research settings, subjective therapies reported by patients with TBI and their families, and subjective clinician case reports.

Numerous clinical studies involving individual nutrients for brain injury treatment in animal models was found and 10 articles summarizing the most prominent of these studies were focused on. The Institute of Medicine (IOM) book about nutrition and TBI[3] was also relied upon for a summary of research in this area. Three specific case reports are highlighted in this article because they represent the most successful alternative treatment approaches for patients with TBI to date. The Brain Trauma Foundation, Brain Health Education and Research Institute, Brainline.org, TraumaticBrainInjuryatoz.org, the National Center for PTSD [post-traumatic stress disorder], and Harch Hyperbarics also supplied information about therapies and treatments that patients with TBI and their families are finding helpful for recovery.

METHODS: A NEW MEDICAL PARADIGM

A new medical model of care, known as functional medicine, is currently gaining acceptance and interest. The functional medicine movement began in the 1960s, when the estrogen receptor was discovered. The subsequent discovery in the 1970s of a diagnostic assay that detected this receptor in tissue, combined with the development of targeted drug therapy by AstraZeneca, marked the birth of the ''personalized medicine'' movement.[4]

The Institute of Functional Medicine defines functional medicine as ''a personalized, systems-oriented model that empowers patients and practitioners to achieve the highest expression of health by working in collaboration to address the underlying causes of disease.''[5] In practice, functional medicine combines conventional Western methods with complementary, genetic, holistic, and nutritional therapies. The functional medicine model, however, is *not* a replacement of conventional medicine as we know it, but rather an all-encompassing medical approach that is included in an increasing number of medical residency programs and sought after by patients.[6,7]

The distinguishing aspect of functional medicine is the fact that functional medicine is used to assess the patient as a whole person, taking into account the interconnectedness of the body and its unique reaction to disease, injury, and illness. Functional medicine focuses on identifying the dysfunctional systems that underlie symptoms and works to restore balance and optimal health. In addition to conventional testing methods, functional testing methods evaluate individual imbalances of detoxification, digestive, hormonal, immune, inflammatory, microbiologic, mitochondrial, neurotransmitter, oxidation, and structural pathways.

Functional medicine evaluations include taking a detailed medical history, while also exploring attitudes, experiences, and emotional and spiritual beliefs. Functional medicine practitioners delve into social, family, and childhood history; environmental exposures; dietary habits; medication and supplement use; exposure to illegal drugs, alcohol, and tobacco; gastrointestinal health; allergies; dental history; and lifestyle. After assessing a patient's history and current symptoms, the clinician will order both routine and specialty tests as indicated. Specialty tests often require an independent laboratory and can include adrenal function, gastrointestinal health, and genetic, toxic metal, and neurotransmitter testing among others.

A comprehensive, whole-body treatment plan is then developed that is specifically tailored to the individual. Conventional prescription medications, holistic therapies, nutritional supplements, and mind–body techniques are incorporated into a treatment plan individualized for the patient. Functional medicine treatment recommendations frequently include: acupuncture; Ayurveda; chiropractic manipulation; detoxification programs; herbal and homeopathic supplements; specialized diets; massage; meditation and mindfulness practices; neurobiofeedback; nutritional supplements; physical therapies; *tai chi*; and yoga.

FUNCTIONAL MEDICINE TBI CASE STUDIES

Case Study 1

Introduction. A teenager involved in a motor vehicle accident suffered severe injuries, including a TBI, with a very poor prognosis of survival. The severity of his injury was assessed using two different evaluation methods: the Glasgow Coma Scale (GCS) and the Ranchos Los Amigos Scale. The GCS is a 15-point scale that associates symptoms with scale levels. A GCS score of 13–15 indicates mild TBI symptoms. A GCS score of 9–12 indicates moderate disability. A GCS score of 3–8 indicates severe disability, and <3 indicates a vegetative state. The Ranchos Los Amigos Scale measures symptoms on a scale ranging from Level I as no response to Level VIII with purposeful and appropriate behavior and actions. Level V is confused and inappropriate behaviors.[8] Lewis et al. reported: ''His GCS was three and computerized tomography (CT) revealed panhemispheric right subdural and small temporal epidural hematomas and a three millimeter midline shift.''[9] An emergency craniotomy was performed with placement of an intracranial pressure monitor. He was started on enteral feedings. The patient was rated as Level I on the Ranchos Los Amigos Scale, and he was not expected to survive his accident. Ten days after his injury, ''T2 weighted magnetic resonance imaging (MRI) revealed right cerebral convexity subdural hemorrhage and…diffuse axonal injury.''[9]

Methods and results. A tracheotomy and a percutaneous endoscopic gastrostomy (PEG) tube were placed and enteral feedings were started for custodial care due to his poor prognosis for recovery. At this time, 9756 mg of eicosapentaenoic acid (EPA) and 6756 mg of docosahexaenoic acid (DHA) were started twice per day, for a total of 19,212 mg of n-3 fatty acids (n-3 FAs) daily via his PEG. Twenty-one days after his injury, he was weaned off the ventilator. On day 24, he had improved enough to be sent to a specialized rehabilitation institute. His Ranchos Los Amigo Scale assessment improved to Level III. Therapy was started and he began to improve cognitively and physically. Three months after his injury, he was able to attend his high school graduation and was discharged to home after 4 months. He remained on 19,212 mg of n-3 FAs with 6000 international units (IU) of vitamin D_3 daily for more than 1 year with no apparent side-effects. Two years later, he was reported to be at Ranchos Los Amigos Level VIII but still experienced speech and balance issues.

Conclusion. After stabilization from the initial trauma and the implementation of enteral feedings, this case indicates that use of high doses of n-3 FAs and vitamin D_3 could be effective additions when treating patients with severe traumatic injury.[9]

Case Study 2

Introduction. A 17-year-old teenager sustained a severe TBI in a motor vehicle accident after being ejected 10 feet from her car. Per Matthews et al., she was unresponsive, had a GCS score of ''5 out of 15,'' and relevant physical examinations findings included a ''blood pressure of 105/56 mmHg, pulse of 87 beats/minute, temperature of 37.7°C,'' and a ''respiratory rate of 20[breaths]/minute.''[10] She was put on a ventilator and had ''unequal pupils with discordant reactivity. Her right pupil was 8 mm and nonreactive to light and her left pupil was 3 mm and reactive to light.''[10] She also has ''decerebrate posturing of both upper and lower extremities bilaterally.''[10] Her CT scan showed ''multifocal, punctuate brain hemorrhages, consistent with a diffuse axonal injury.''[10]

Methods and results. Upon this patient's admission to the surgical intensive care unit, 50,000 IU of vitamin D_3, 20 mg of progesterone, 2 g of n-3 FAs, and 20 g of enteral glutamine were started via a nasogastric tube. Within 24 hours, her decerebrate posturing resolved. By day 3, she was able to follow simple commands when sedation was stopped. She was extubated on day 9 and discharged to an inpatient rehabilitation facility by day 18. Her GCS score improved to 15, and she was able to return to school within 3 months of her accident.

Conclusion. This case supports further research into the use of vitamin D_3, progesterone, n-3 FAs, and glutamine offer promising outcomes as part of a TBI treatment plan.[10]

Case Study 3

Introduction. A 25-year-old military veteran was seen 3 years after exposure to an initial blast injury during combat for evaluation and possible treatment with hyperbaric oxygen therapy (HBOT). At the time of his initial injury, he experienced short-term confusion and memory loss. Three months after his exposure to the initial blast, he was diagnosed with PTSD and later with post-concussion syndrome (PCS). During his subsequent tours of duty over the next 15 months after the initial blast, he was exposed to six more explosions. At his HBOT evaluation he reported continued symptoms of tinnitus, headaches, and sleep disturbances.

Methods and results. Per Harch et al., the patient underwent ''single photon emission computed tomography brain blood flow imaging before and after a block of thirty-nine 1.5 atmospheres absolute hyperbaric oxygen treatments.''[11] His PTSD symptoms completely resolved and his PCS symptoms were reduced significantly after 39 treatments of low-dose hyperbaric oxygen treatments.

Conclusion. This case supports further research into the use of HBOT treatments for treatment of PCS and PTSD.[11]

DISCUSSION

Functional Medicine Approach to TBIs

A TBI occurs after a blunt force trauma to the head. Symptoms of an injury include, among others, loss of consciousness or memory, headache, vomiting, loss of balance, change in vision, slurred speech, or sudden confusion. The GCS is one scale used to assess the severity of a brain injury. Mild TBIs (mTBIs) are considered to be more difficult to diagnose, with no standardized criteria. During the initial injury, surgical and/or intensive care is given, depending on the severity with the goal of maintaining adequate oxygenation and controlling intracranial pressure. A cascade of secondary and ongoing injuries can then progress due to neuro-inflammation, excitatory amino acids, free radicals, abnormal calcium homeostasis, and ion imbalance. Glucose metabolism can also be impaired, with glutamate and aspartate levels becoming excessive.[12]

The Veterans Administration (VA) and DoD established practice guidelines for treatment of mTBI and other comorbidities. These guidelines include use of appropriate rehabilitation techniques dependent on symptoms, medications, mind–body interventions, sleep hygiene interventions, cognitive–behavioral therapy (CBT), CBT for insomnia, a white-noise generator, and repetitive transcranial magnetic stimulation.[13]

However, effective treatments for the secondary injury cascades that occur after initial brain trauma is less clear. The goal of successful treatment options for secondary TBI injuries linked to progressive degeneration is to ''reduce oxidative stress by reducing oxidation of lipids, proteins, and DNA; reduce excitotoxicity by controlling excess levels of brain glutamate; reduce inflammation by reducing inflammatory cytokines and activated microglia; increase mitochondrial energy production by supporting mitochondrial functions; and repair membranes, synapses, and axons with dietary lipids.''[14,15]

Few clinical trials and empirical studies show consistent benefits from the use of alternative TBI treatments. However, therapies that warrant further investigation based on positive results from research studies, case histories, antidotal evidence, and widespread popularity include acupuncture; Ayurveda; electroencephalograph therapy and HBOT; chiropractic manipulation; CranioSacral therapy, art and recreation therapies; herbal and homeopathic supplements; ketogenic diet; massage; meditation and mindfulness practices; neurobiofeedback; nutrition; *t'ai chi*; and yoga.[16] To date, the use of nutritional therapy and HBOT show the most promising outcomes for treatment of secondary TBI injuries.

Often, a functional medicine practitioner will see a patient with a TBI years after the initial injury. Each patient with TBI will be assessed using a functional medicine questionnaire and regular and specialty testing as indicated. A treatment plan is then formulated that addresses each area of concern and changes are made one step at a time with results monitored closely. Diet concerns will usually be addressed first. The patient will be sent to a registered dietitian to address deficiencies in the diet and to develop a realistic plan that provides a balanced diet rich in omega-3 fatty acid foods and fruits and vegetables to supply antioxidants. The diet recommended will also be low in added sugars and processed foods. A probiotic may be recommended to ensure a healthy microbiome, given that the quality and balance of gut bacteria is increasingly linked to brain health.[17] However, probiotic use requires further evaluation as probiotics can be contraindicated with specific medical conditions.

Special diets, such as gluten- and dairy-free diets, might be indicated when inflammation is a concern. Ketogenic diets might be recommended, as some data indicate positive improvements. Glucose is the usual source of energy for brain cells. Because the injured brain often has impaired glucose utilization, ketones can be used as an alternative fuel for neurons that are not transporting glucose effectively. The presence of ketones in the body's circulation has been shown to increase cerebral blood flow by as much as 40%. Monocarboxylate transporters (MCTs), found in MCT oil or coconut oil, appear to improve glucose utilization by the brain. Coconut oil used as a source of ketones can reduce free-radical generation, increase production of endogenous glutathione, and act as an anti-inflammatory agent (Steve Haltiwanger, MD, CCN, personal communication).[18]

Neurotransmitter imbalances in TBI patients might also be assessed. Neurotransmitter imbalances in the brain appear to be linked to the cascade of secondary TBI injuries. One neurotransmitter, dopamine, can be excitotoxic when levels are excessive. Treatments that support dopamine-signaling pathway regulation may reduce oxidative stress and improve functional outcomes.[19]

Genetic testing can also be of benefit when identifying effective treatments for a specific individual. To date, genes identified with TBI outcomes include ''*apoE4* and *apoE* promoter genes, calcium channel subunit gene, *p53* gene, catechol-o-methyltranserase gene, D_2 receptor gene, and genes coding for the production and metabolism of interleukins, hemeoxygenase-1 (HO-1), and angiotensin-converting enzyme.''[20] The presence of the *apoE4* allele has been found in some studies to be associated with reduced outcomes after severe TBI. The calcium-channel gene affects calcium homeostasis, which is impaired in brain injuries. The COMT and D_2 receptor genes affect neurotransmitter activity and the genes that control interleukins, hemeoxygenase-1, and angiotensin converting enzyme, all of which may control inflammation that can lead to negative outcomes after a brain

injury. However, it is important to note that genetic testing as a medical tool is still in its infancy and is not yet understood clearly when the results are applied as a treatment option. Results should be interpreted with caution.

Nutrition Therapies for TBI

We do know that nutrition therapy, when combined with other TBI treatments, is very effective during initial brain trauma. The DoD's Military Nutrition Division of the U.S. Army Research Institute of Environmental Medicine in conjunction with the IOM published a report in 2011 evaluating the use of nutrition therapy for TBIs. Evidence shows consistently that nutritional intervention can reduce risk of mortality and ongoing progressive damage. A Cochrane Collaboration review of studies in 2006 (cited in an IOM report) found that early feeding of severe patients with TBI that delivered >50% of the patient's total energy expenditure and 1.0–1.5 g of protein per kg of body weight resulted in improved recovery and decreased mortality if nutritional support was implemented within 24 hours after injury and continued for at least the first 2 weeks after injury.[21]

This has led to the investigation of other nutrition therapies for the treatment of secondary injuries. One nutrition therapy that continues to show benefits for patients with TBI in research studies is the use of omega-3 fatty acids (n-3 FAs). N-3 FAs are a group of polyunsaturated fats. N-3 FAs are comprised of EPA and DHA (from fish sources) and alpha-linoleic acid (ALA) and linolenic acid (found in plant food sources). Use of n-3 FAs in TBI is of particular interest because the brain is rich in polyunsaturated fatty acids, with DHA concentration in the phospholipids of neuronal plasma membranes and synaptic vesicles. It is well-recognized that n-3 FAs are required for ideal neuro-development and function. Research shows n-3 FAs have anti-inflammatory properties and can be cardioprotective, especially against sudden death from arrhythmias.[22] The American Heart Association recommends that every American eat a 3.5-ounce serving of fish at least 2 times per week or take 3 g of an omega 3 fatty-acid supplement to support a healthy heart.[23] N-3 FAs have also been shown in some studies to reduce muscle soreness and increase rates of recovery while reducing inflammation and oxidative stress after exercise. However, more research is needed in this area to validate these findings.[24]

Supplementing with n-3 FAs appears to provide an anti-inflammatory and neuroprotective effect for brain cells and neurons. N-3 FAs also appear to support the control of secondary injury cascades. N-3 FAs appear to play a role in ''reduction in excitotoxicity, modulation of calcium and potassium channels, activation of gene transcription, and formation of neuroprotectin-1 and resolvins.''[25]

Using n-3 FAs as a possible treatment option for brain injury first came to national attention during the Sago Coal Mine Explosion in 2006. The only survivor, Randal McCloy Jr., was exposed to ~40 hours of toxic carbon monoxide and methane gas levels. He suffered from hypoxia, dehydration, a massive heart attack, kidney and liver failure, hypothermia, and a brain hemorrhage. In a coma, his prognosis for survival was poor. Seen by neurosurgeon Dr. Julian Bailes and Barry Sears, MD, he was started on nutritional feedings immediately after he was stabilized and given HBOT treatments. Some improvements were noted and he was given hemodialysis for 7 days. His tube-feeding formula was changed to one that provided 5 g of n-3 FAs (3.4 g of EPA and 1.7 g of DHA), glutamine, and arginine daily on day 2 after his injury. In addition to the n-3 FAs in his enteral feeding, 16.2 g of n-3 FAs (10.8 g of EPA and 5.4 g of DHA) were added to his daily feedings on day 8. By day 30, he was receiving a total of 10 g of n-3 FAs daily. It is unknown how long he continued to take n-3FAs after discharge from the hospital on day 21 to a rehabilitation facility. He continued to improve and, 1 year later, showed steady improvements with residual deficits and need for continued therapies.[26]

Although this case did not involve a TBI, it did highlight the possible use of n-3 FAs and HBOT therapy as part of an effective treatment plan for injured brains.

Michael Lewis, MD, MPH, MBA, FACPM, is the founder and president of the Brain Health Education and Research Institute, a retired U.S. Air Force Colonel, and author of the book chapter ''It's Never Too Early: Omega-3s as Preventative Medicine.''[27] Dr. Lewis is considered a pioneer in the use of omega-3s for the prevention, management, and treatment of TBIs and explores omega-3 research in his book.[27]

In addition to n-3 FA's, combinations of different nutrients and hormones also show promise for TBI treatment. Supplementing with vitamin D and progesterone, both steroid hormones, and n-3 FAs show an anti-inflammatory and neuroprotective effect while also reducing cerebral edema and improving neuron response to stress. Adding glutamine, which is utilized as an essential amino acid during stress, also produces extra glucose that is then utilized by the injured brain to fight infection.[10]

Physician and clinical nutritionist, Dr. Steve Haltiwanger, MD, CCN reports that he uses nutrition therapies routinely with his patients who have TBIs. He emphasizes that nutrients must be able to pass through the blood–brain barrier and metabolic energy support must be started as soon as possible after the primary injury for nutritional therapies to be effective. He presented his TBI nutrition protocol at the 2014 International and American Association of Clinical Nutritionists Symposium. Based on his work with patients who have TBIs, he routinely begins all of his patients on ALA, acetyl-L-carnitine, coenzyme B complex, methylated vitamins B_{12} and C, choline, curcumin, vitamin D_3, DHA, lipoic acid, magnesium glycinate, melatonin, niacinamide, and oxaloacetate supplementation. Review of studies show that some of these nutrients appear to support myelin repair, modulate anti-inflammatory cytokines, reduce lipid

Table 1. Alternative Treatments for TBI

Treatment	*Comments & references*
Acupuncture & acupressure	The few studies performed have shown some benefits. However, the studies had a high risk of bias & minor adverse events were frequently reported.[16,28]
Hyperbaric oxygen therapy	Breathing pure oxygen under pressure overwhelms red blood cells, saturating blood plasma & other body fluids with oxygen & stimulating release of growth factors & stem cells, which promote healing. Excess oxygen also supports revascularization of injured sites & appears to decrease healing time. More research is needed, however, as reported results have not been validated.[28]
Mindfulness-based cognitive therapy, including Qigong, *t'ai chi* & yoga	Preliminary studies show improvements for TBI, but more research is needed.[28]
Music therapy	Initial study results for patients with TBI appear positive. However, risk for bias is high & further studies are needed.[28]
Nutrition therapies	
Antioxidants	Use of combined antioxidants could decrease ROS damage immediately after injury.[18]
Branched-chain amino acids	Branched chain amino acids are precursors of neurotransmitters. Their use may possibly affect neurotransmitter imbalances in the brain. However, research has not yet supported use for TBI.[18]
Choline	This is an anti-inflammatory & antioxidant that could support a decrease in calcium-mediated cell death, which is common in TBI.[18]
Coenzyme Q10	This nutrient shows a positive effect against neurodegenerative & mitochondrial disorders.[29]
Creatine	This nutrient could improve cognition & behavior, maintain mitochondrial function & improve cerebral vascular function, which is common during the initial, acute phase of TBI.[18]
Curcumin	There is some evidence of improved motor & learning performance, blood–brain barrier integrity, cognition & reduced cerebral edema in brain injured animals.[18]
Glutathione	There is some evidence that this nutrient reduces ROS levels & improves brain injury markers.[30]
Ketogenic diet	Some evidence provides an alternative energy source that reduces brain dependence on glucose metabolism that is impaired after a TBI.[18]
Lipoic acid	This is an antioxidant that might reduce lipid peroxidation. Animal research shows that it might reduce neuron death after TBI.[31]
Magnesium	This mineral is usually depleted in TBI. It could have a neuroprotective effect & decrease glutamate damage by regulating calcium entry into postsynaptic neurons.[18]
Melatonin	Decreased levels common after mTBI appear to affect sleep patterns. Supplementation may reduce sleep-cycle disruptions.[32]
N-3 fatty acids (EPA and DHA)	Evidence shows an anti-inflammatory & neuroprotective benefit against brain injuries. Research is not conclusive, however.[18]
Polyphenols	These nutrients have anti-inflammatory properties.[18]
Vitamin D	This vitamin binds DNA response involved in regulation of gene transcription, differentiation & neural function in the brain.[33]
Vitamin E	This vitamin reduces oxidative stress & improves cognition, memory & learning in animal studies.[18]
Vitamin K_2	This vitamin is neuroprotective.[34]
Zinc	This mineral is required in central nervous system enzyme functions. Zinc is released in the synaptic cleft of the brain where neuroreceptor activity is modulated. Excess release of zinc contributes to neural cell death. Zinc deficiency could exacerbate cell death in TBI. Patient trials with zinc show positive effects in severe closed-head injuries. More research is indicated.[18]
Progesterone	This is a steroid hormone that has neuroprotective effects on injured brain cells & potentiates the effect of vitamin D. Combined use of vitamin D with progesterone requires further study.[18]

TBI, traumatic brain injury; ROS, reactive oxygen species; mTBI, mild traumatic brain injury; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

peroxidation, reduce inflammation, oxidative stress, and excitotoxicity, and support mitochondrial function.

In addition to supplementation, Dr. Haltiwanger encourages his patients to consume a daily diet rich in complex carbohydrates, omega 3 fatty acids, raw vegetables, fruits that have a high oxygen radical absorbance capacity value (i.e., blueberries), and coconut oil. He recommends avoidance of alcohol, processed foods, highly sugared foods and drinks, and use of sugar substitutes such as aspartame. In addition, he recommends 2 tbsps. of MCTs or coconut oil 1–3 times daily (S. Haltiwanger, personal communication). While Dr. Haltiwanger reports success in his practice with this TBI protocol, objective research is still needed in this area to substantiate his results.

Table 1[16,18,28–34] provides a summary of nutrition therapies that could be of benefit in TBI treatment.

Hyperbaric Oxygen Therapy for TBI

The brain is one the largest consumers of oxygen in the human body. Injured brain tissue requires even more oxygen to survive. HBOT increases the amount of oxygen blood can carry and may temporarily restore normal levels of blood gases and tissue function and help to promote healing and fight infection. HBOT is primarily used in the United States for healing acute and chronic wounds and some infections because of its effect on blood-vessel, connective tissue, bone, and skin growth. It has been recognized since the 1930s that breathing pure oxygen alters signaling pathways and promotes angiogenesis involved in wound repair. Burn centers use HBOT routinely to speed up healing time and the U.S. Food and Drug Administration approved HBOT for use in treating carbon monoxide poisoning, radiation burns, crushing injuries, and smoke inhalation.

HBOT is defined as ''a therapy of increased total atmospheric pressure and partial pressure of oxygen over ambient total and oxygen partial pressures.''[35] The patient is exposed to gradual air pressurization up to three times higher than normal air pressure, allowing the lungs to breathe in up to three times more oxygen than possible at normal air pressure. Pure oxygen is breathed for 1 hour or more. Breathing pure oxygen under pressure overwhelms red blood cells, saturating blood plasma and other body fluids with oxygen and stimulating release of growth factors and stem cells, which promotes healing. Excess oxygen also supports the revascularization of injured sites and appears to decrease healing time.

DoD studies on the effectiveness for HBOT with mTBI have had mixed results. Paul Harch, MD—a prominent HBOT researcher, president and chairman of the International Hyperbaric Medical Foundation, and author of ''*The Oxygen Revolution*''[36]—and his colleagues reported a clear therapeutic benefit for the use of HBOT in patients with mTBI as well as those with persistent PCS.

His 2012 study of U.S. war veterans with TBI and PTSD found that, after 40 low-pressure hyperbaric oxygen treatments over a 1-month period, study participants achieved significant reductions in symptoms, and improvements in physical examinations, cognitive testing, quality of life, and brain blood flow. In addition, a 50% reduction in depression symptoms and a significant reduction in suicidal ideation, with reductions in psychoactive medication use by almost two-thirds of veterans who were using these medications were all reported. Computer imaging showed that the hippocampus— responsible for short-term memory and the first area of the brain usually injured—showed significant improvements in blood flow after 1 HBOT treatment and significant improvements in memory after 40 treatments. However, the study sample size was small and totaled 16 active duty or retired service members. The DoD has also raised questions regarding the validity of research results in this area. More research is still needed into the potential benefit of HBOT treatment for brain-injured patients.[37]

CONCLUSIONS

TBIs are of major concern in the U.S. military because of their major public health impact and cost. Trauma to the brain begins a cascade of secondary injuries that continue to occur after the initial effects of injury. Effective treatments for these secondary injuries of TBI are elusive, and many patients and their families have turned to alternative treatments.

A new medical paradigm—functional medicine—is gaining acceptance in the medical community and is increasingly sought after by patients. The functional medicine approach to TBI treatment assesses the individual as a whole, combining conventional treatment with therapies that are aimed to reduce inflammation, support methylation pathways, manage neurotransmitter and mitochondrial imbalances and toxic overload, support myelin repair, decrease lipid peroxidation, and reduce nutritional deficiencies. To date, only nutritional therapies and HBOT show the most promise for treating secondary TBI injuries. However, few clinical trials have been performed with these alternative treatments, and those that have been performed have produced inconclusive results.

The IOM, at the request of the DoD, investigated nutritional therapies that appeared promising for treating brain trauma. Nutrients selected for further investigation were chosen based on their potential role for reducing oxidative stress and inflammation while supporting repair and recovery from injuries. The following nutrition interventions were selected for further study: ''energy needs, acetyl CoA [coenzyme A], antioxidants, branched-chain amino acids, choline, creatine, ketogenic diets, magnesium, nicotinamide, nicotinamide adenine dinucleotide+, n-3 FAs, polyphenols,

probiotics, vitamin D, and zinc'' and combined nutrient protocols. Resveratrol, curcumin, and progesterone were highlighted as potentially beneficial and also worthy of further study. Concern about potential harm from use of acetyl-L-carnitine, niacin, and probiotics was noted and these nutrients were excluded from further review as of 2011. The IOM also emphasized further evaluation of the effect of blood glucose levels on the injured brain and glucose management. Further research into ketones and the ketogenic diet was advised. Diet evaluation of all military personnel pre- and post-deployment to provide a baseline nutrition status was recommended to better evaluate the effectiveness of nutrient interventions in patients with TBI.[3]

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