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Review Article

Nutritional Support Following Traumatic Brain Injury: A Comprehensive Review

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Abstract

Traumatic brain injury (TBI) can contribute to extensive dysbiosis of the gastrointestinal system, leading to worsened outcomes. The importance of nutrition in recovery is underappreciated but highly important. In this focused review, we discuss the timing of nutritional interventions with supporting data. We highlight routes of administration that are important given the extent of injury often seen in TBI. The increased energy demands can be met through these approaches. Furthermore, patients need increased vitamins, minerals, and supplements. These interventions are constantly being refined. The current standards are reviewed with an emphasis on evidence-based practices.

Introduction

Traumatic brain injury (TBI) is a leading cause of death globally.[1] The estimated economic cost of TBI in the United States was 76.5 billion dollars in 2010.[2] Additionally, it is estimated that 5.3 million Americans who suffer from TBI are burdened with long-term disability and increased dependence.[3,4] Pharmaceutical agents that target facets of TBI pathophysiology have demonstrated limited efficacy.[5] A growing area of interest in understanding TBI pathophysiology is the role of nutritional support in mitigating TBI sequelae.

Nutritional support is essential given that the human brain consumes 20% of total resting energy despite accounting for only 2% of total body mass.[6] Malnutrition in critically ill patients promotes endocrine dysfunction, multiorgan failure, impaired immunity, and increased mortality. Nutritional therapy aims to prevent malnutrition and its complications. Alterations in metabolism and gastrointestinal dysfunction contribute to the nutritional deficits seen in TBI and other neuroinflammatory conditions such as sepsis, stroke, and coronavirus disease 2019 (COVID-19). Moreover, these nutritional deficits are often coupled with poor functional outcomes.[7–11] Thus, optimization of nutritional care in critically-ill patients is needed to improve short- and long-term recovery. Additionally, studies highlighting an increased prevalence of malnutrition among TBI patients further emphasize the importance of adequate nutritional support post-TBI.[9,12–15] Likewise, timing and route of nutritional therapy are also essential to treat TBI.[16]

Generally, TBI injuries are classified as primary and secondary injuries. The primary injury of TBI involves mechanical damage to the central nervous system (CNS). It is typified by tissue deformation, axonal shearing, and blood-brain barrier (BBB) dysfunction. The secondary injury of TBI, which occurs in response to the initial primary injury, is typified by cerebral edema, increased inflammatory cytokines, excitotoxicity, ischemia, reactive oxygen species, and immunosuppression.[17] Together, these injuries affect cellular metabolism by creating a hypermetabolic and hypercatabolic state that ultimately increases caloric expenditure among TBI patients (Fig. 1).[16,18,19] The increase in caloric expenditure is associated with increased lean body mass consumption, negative nitrogen balance, electrolyte imbalance, increased susceptibility to infections, longer hospital stays, and increased morbidity and mortality.[18,20,21] Thus, optimal nutritional support post-TBI may

Keywords: Nutrition; Traumatic brain injury; Supplements; Vitamins; Minerals.

Abbreviations: ARDS, acute respiratory distress syndrome (ARDS); ATRA, all-trans retinoic acid; BBB, blood-brain barrier; BNDF, brain-derived neurotrophic factor; BrdU, Bromodeoxyuridine; COVID-19, coronavirus disease 2019; CSWS, cerebral salt-wasting syndrome; CNS, central nervous system; DHA, docosahexaenoic Acid; GDNF, glial cell line-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; IGF-1, insulin growth factor 1; NAD+, nicotinamide adenine dinucleotide; NGF, nerve growth factor; NCAM, neuronal cell adhesion molecule; NSC, neural stem cell; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; Nogo-A and Nogo-B, neurite outgrowth inhibitor- A, B; Nrf2, nuclear factor erythroid 2-related factor 2; PEG, percutaneous enteral gastrostomy; PYC, Pycnogenol; RCT, randomized controlled trial; REE, resting energy expenditure; SIADH, syndrome of inappropriate antidiuretic hormone; Sir2, silent information regulator 2; SOD, superoxide dismutase; TN-C, tenascin-C; TBI, traumatic brain injury.

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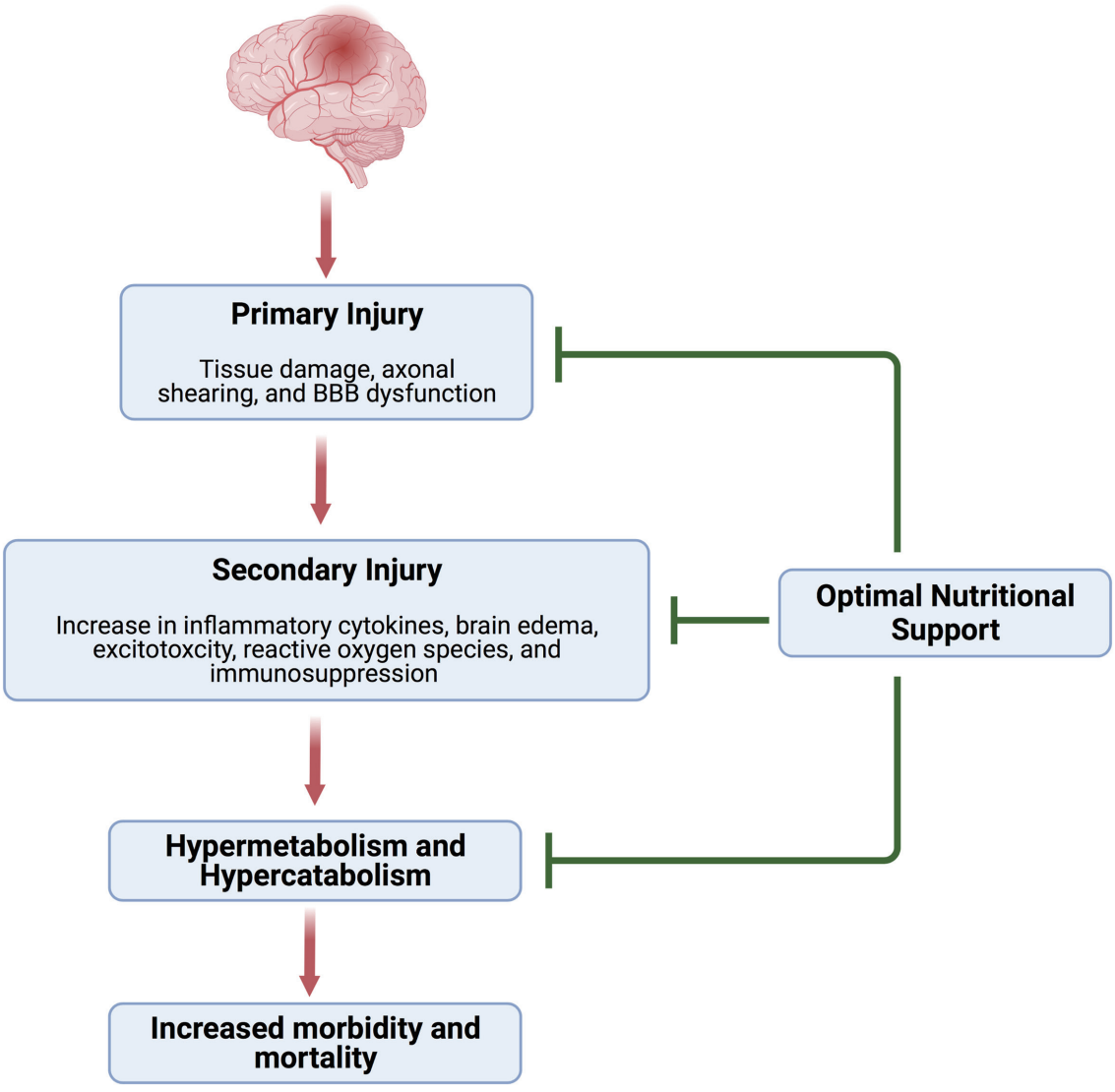

Fig. 1. Schematic representation of traumatic brain injury (TBI). TBI causes primary and secondary injury. The primary injury results from the initial mechanical insult and is characterized by tissue damage, axonal shearing, and blood-brain barrier (BBB) dysfunction. The secondary response is initiated minutes to hours after TBI and is characterized by increased inflammatory cytokines, brain edema, excitotoxicity, reactive oxygen species (ROS), and immunosuppression. These alterations promote a hypermetabolic and hypercatabolic state that increases morbidity and mortality post-TBI. Optimal nutritional support post-TBI is a potential strategy to meet the increased metabolic demand associated with TBI. Image credit: BioRender.

be critical in mitigating the hypermetabolic and hypercatabolic responses associated with TBI. This review provides an overview of nutritional support following TBI and highlights promising findings of preclinical and clinical nutraceutical interventions that warrant future investigations.

Timing of nutritional support post-TBI

Early initiation of nutritional support following TBI is crucial in offsetting the acute catabolic state seen in TBI.[18] Early nutrition supports the preservation of muscle mass, decreases infection complications, promotes cerebral homeostasis, and improves functional outcomes.[22–24] Ideally, nutritional support should be started within 24–48 h post-TBI to provide 50% of resting energy expenditure (REE) within the first two weeks post-injury. Previous studies have also shown that patients with TBI need about 100–150% of REE. The REE is ideally measured by indirect calorimetry. If the measurement of REE is not possible by indirect calorimetry, administration of 25 kcal/kg/day, or 70% of the measured or estimated REE during the initial 7 to 10 days, is advised.[25] In a recent study, failure to initiate nutritional support within 5–7 days post-TBI was associated with increased mortality by 2 to 4 folds.[26] Though early initiation of nutritional support is vital post-TBI, it is also essential to consider that overfeeding may result in metabolic issues such as refeeding syndrome with electrolyte derangements. Furthermore, it is crucial to note that TBI patients may experience some difficulty maintaining caloric intake due to pain, loss of appetite, and other co-injuries that include facial fracture, oral injuries, and cervical immobilization.[27,28]

Nutritional requirements following TBI

When considering nutritional requirements after TBI, it is crucial to determine the optimal glucose, protein, and lipid concentrations needed for neuronal survival.[28] Hyperglycemia and hypoglycemia can occur in TBI patients.[21,29,30] Hyperglycemia is more common post-TBI and is thought to be caused by increased insulin resistance and worsening stress metabolism.[31,32] This rise in blood glucose is associated with worsened outcomes post-TBI.[30] Studies have demonstrated that blood glucose control with insulin therapy improved post-TBI outcomes; however, intensive insulin therapy compared to conventional insulin therapy worsened post-TBI outcomes, especially in patients with severe TBI.[33–36] The suggested optimal blood glucose level post-TBI is 6–9 mmol/L (108–162 mg/dL).[37,38]

Patients with severe TBI may lose 10–15% lean body mass in a week without adequate nutrition.[39] Protein catabolism is a major contributor to this loss, and is increased significantly in the acute phase of TBI, appears to peak at 8–14 days, and is related to TBI severity.[40] Nitrogen excretion post-TBI is estimated to range from 0.2 to 0.28 g/kg/day.[41,42] Aggressive supplementation with protein to mitigate nitrogen loss and maintain muscle mass is ineffective in reversing TBI's catabolic state.[43,44] However, current guidelines recommend the early provision of 1.5 to 2.0 g/kg/day of protein in TBI patients.[28] Adequate free water should be provided to patients on these high protein diets to prevent azotemia, especially in patients with renal insufficiency.[28] Anabolic hormone insulin growth factor 1 (IGF-1) has demonstrated promising results in restoring a positive protein balance post-TBI in patients receiving growth hormone.[45] However, the use of growth hormone and IGF-1 in the management of critically ill patients is controversial, given that some studies have demonstrated increased mortality in critically ill patients treated with growth hormone.[46,47]

Monitoring fluid and electrolyte requirements are essential for caring for TBI patients. Immediately after TBI, patients may experience episodes of hypotension, often requiring intravenous fluid resuscitation.[48–50] Patients treated with osmotic diuretics such as mannitol should be monitored for fluid depletion and resuscitated if needed. The ideal fluid (colloids versus crystalloids) to be used post-TBI is not well established.[28,51] Consideration of fluid type requires extensive knowledge of the advantages and disadvantages of using that fluid. A large randomized controlled trial (SAFE-TBI) demonstrated that 4% albumin significantly increased mortality in TBI patients compared to patients that received normal saline (0.9% sodium chloride).[52] Despite the SAFE-TBI findings, there is still some support for the continued use of albumin in treating TBI patients; however, the addition of crystalloid solution is encouraged. Additionally, when using albumin, clinicians are cautioned to use high concentration solutions, infuse at low rates, avoid high blood pressures and vasopressors, avoid low hemoglobin concentrations, and encourage frequent physiotherapy to activate the lymphatic recirculation system.[51]

As with albumin, intravenous dextrose should be used with caution in the acute phase of TBI due to an increased risk of hyperglycemia.[53] While fluid resuscitation is essential, TBI patients must not receive excessive fluids as this may worsen brain edema and increase the risk for hemodilution, acidosis, and acute respiratory distress syndrome (ARDS).[51,54,55] Electrolyte repletion in patients with TBI is vital. Hypotonic solutions should be avoided in patients with hyponatremia. Hyponatremia is very common in TBI patients and is often caused by cerebral salt-wasting syndrome (CSWS) or the syndrome of inappropriate antidiuretic hormone (SIADH) release. If hyponatremia is not adequately treated, hyperchloremic acidosis may ensue. On the other hand, if treated too aggressively with osmotic diuretics, pronounced hypernatremia may ensue. Other electrolytes that require monitoring post-TBI include potassium, magnesium, calcium, and phosphate.[51] Daily nutritional requirements post-TBI are shown in Table 1.

Table 1. Energy requirements following traumatic brain injury (TBI)

Glucose requirements	
Glucose	2–3 g/kg/24 h
Protein requirements	
Protein	1–1.5 g/kg/24 h
Lipid requirements	
Lipid	0.5–2 g/kg/24 h
Electrolyte requirements	
Sodium	1–1.4 mmol/kg/24 h
Potassium	0.7–0.9 mmol/kg/24 h
Phosphate	0.15–0.30 mmol/kg/24 h
Magnesium	0.04 mmol/kg/24 h
Calcium	0.11 mmol/kg/24 h

The table was adapted from Sundstrøm's research.[51]

Routes of nutritional support post-TBI

The route of nutritional support is an important consideration following the stabilization of vitals and intracranial pressure in patients with TBI. Many TBI patients face difficulties with swallowing, and some may require mechanical ventilation; thus, the enteral nutritional route is the preferred method of nutritional support, especially within 24–48 h post-TBI.[28] Enteral formulas with partially digested fats and proteins are preferred over non-digested formulas due to their ability to enhance gastric emptying and digestion.[20] Furthermore, early enteral nutrition has been shown to significantly decrease mortality, the risk of metabolic derangements, pressure ulcer formation, and hepatobiliary dysfunction in TBI patients.[24,56–58] Several feeding strategies need to be considered when initiating enteral nutrition. First, the patient's head needs to be elevated by 30 to 45 degrees off the bed to decrease reflux.[59] Second, graduated feeding may be attempted in patients initially intolerant to enteral nutrition. These patients can be started initially at 20 mL/h and advanced to their specific goal by 10–20 mL/h every 6–8 h. Furthermore, continuous enteral nutrition is well tolerated compared to bolus enteral nutrition.[28,60]

Enteral nutrition is achieved by passing a tube from the nasal cavity to the stomach or intestine. In the case whereby the patient is on a mechanical ventilator, the tube can be passed from the mouth.[51] Prokinetic agents such as erythromycin and metoclopramide can be used as singular therapies or combined to enhance gut motility in the short term for patients with gut motility dysfunction.[61,62] If the prokinetic drugs are unsuccessful in aiding bowel motility or are not well tolerated, small bowel feeding can be considered over gastric feeding. There is a growing recommendation for small bowel feeding in the acute phase of TBI over nasogastric feeding because small bowel feeding has been shown to reduce the incidence of infections, enhance feeding tolerance, and decrease reflux.[25,63,64] Additionally, if the need for enteral nutrition exceeds 2–4 weeks, percutaneous enteral gastrostomy (PEG) may be preferable.[51]

Although enteral nutrition is the preferred route of nutritional support post-TBI, parenteral nutrition can also be considered if there is a delay in obtaining enteral access or failure to meet nutritional needs within 3–7 days of enteral nutrition and in heavily sedated patients.[33] However, it is important to note that parenteral nutrition increases the risk of hyperglycemia, infection, hepatic steatosis, loss of gut barrier integrity, and immunosuppression.[18] Daily requirements for parenteral nutrition are administered by a three-chamber bag comprising glucose, fats, and amino acids. When starting parenteral nutrition, several important factors must be considered. For instance, it is prudent to use a dedicated nutritional central venous catheter that is separate from those used to deliver medications or fluids. Also, the nutritional line must be inspected frequently.[51,65] A recent retrospective study showed that TBI patients managed with a combination of enteral and parenteral nutrition demonstrated improved clinical outcomes.[66] However, future randomized controlled trials (RCTs) are needed to corroborate this finding.

Vitamins, minerals, and nutritional supplementation post-TBI

Support for using vitamins, minerals, and supplements in treating TBI has increased in recent years.[5,67,68] This section discusses a list of vitamins, minerals, and dietary supplements examined in preclinical and clinical TBI studies. These findings are also concisely summarized in Tables 2 and 3.

Vitamins and Minerals

Vitamin A (retinol)

Although vitamin A supplementation has not been investigated in TBI, a recent study demonstrated a role for the bioactive vitamin A active metabolite, all-trans retinoic acid (ATRA). A study by Hummel *et al*. showed that male adult mice treated with ATRA (10 mg/kg) immediately after TBI and within the first three days post-TBI demonstrated a reduction in lesion size, astrogliosis, axonal injury, and the hippocampal granule cell layer was protected; however, ATRA did not significantly improve neurological and motor deficits.[69]

Vitamin B2 (riboflavin) and magnesium

When administered to rats post-TBI, riboflavin, a powerful anti-oxidant, significantly reduced behavioral impairments, lesion size, edema formation, and expression of the glial fibrillary acidic protein (GFAP).[70] A later study by the same group demonstrated that co-administration of riboflavin (7.5 mg/kg) and magnesium (1 mmol/kg) led to a synergistic improvement in functional recovery compared to individual treatments.[71] Additionally, treatment of magnesium sulfate (30 mg/kg) alone or in combination with n-acetyl L tryptophan (2.5 mg/kg) in rats post-TBI has been shown to alleviate blood-brain-barrier permeability and improve functional outcomes.[72] Clinical studies supporting the use of magnesium after TBI have had mixed results.[73–75]

Vitamin B3 (nicotinamide)

Nicotinamide increases available cellular energy as a precursor to nicotinamide adenine dinucleotide (NAD+), thus alleviating post-injury cellular stress. When administered, nicotinamide (50 mg/kg or 500 mg/kg) provided neuroprotective effects and alleviated behavioral deficits in rodents following TBI.[76–78] Nicotinamide (continuous infusion of 12 mg/kg/h with a loading dose of 75 mg/kg) also demonstrated potential synergistic effects with progesterone with regards to neuroprotection after TBI; however, further investigations are needed to identify the window of opportunity for intervention and treatment duration.[79]

Vitamin B6 (pyridoxine)

Pyridoxine is an essential cofactor involved in several metabolic enzymatic reactions. Additionally, pyridoxine plays a crucial role in the synthesis of brain neurotransmitters.[80] Supplementation of pyridoxine (300 mg/kg or 600 mg/kg) in rats post-TBI demonstrated significant improvement in locomotor behavioral performance compared to vehicle controls. Moreover, the neuroprotective effects of pyridoxine supplementation post-TBI were shown to be dose-dependent. The authors suggested that the benefit of pyridoxine supplementation post-TBI may be related to improved oxygen delivery to damaged tissues, given that pyridoxine has been shown to upregulate erythrocyte affinity for oxygen.[81,82]

Vitamin B9 (folic Acid)

Folic acid is well recognized for its role in fetal neural tube closure during pregnancy.[83,84] Folic acid deficiency has been shown to contribute to impaired cognition and dementia.[85,86] Likewise, supplementation of folic acid after hemorrhagic stroke has been shown to be protective.[87] While the role of folic acid in TBI is limited, an earlier study by Naim *et al*. showed that female piglets post-TBI treated with folic acid (80 µg/kg) demonstrated improved cognitive function in the acute period (day one post-TBI).[88] In contrast, Vonder Haar *et al*. showed that neither low (80 µg/kg) nor high dose folic acid (800 µg/kg) improved behavioral outcomes in adult rats post-TBI. In fact, a high dose of folic acid (800 µg/kg) administered post-TBI in rats increased neuronal loss compared to vehicles.[89]

Vitamin B12 (cobalamin)

Like folic acid, cobalamin plays a critical role in neuronal function.[90] Administration of cobalamin (0.5 mg/kg or 1.5 mg/kg) in male mice post-TBI showed significant improvement in neurological functional recovery. Further experiments demonstrated that the neurological recovery post-TBI in mice treated with cobalamin might be due to the downregulation of the endoplasmic reticulum stress-related apoptosis signaling pathway.[91]

Vitamin C (ascorbic acid)

Ascorbic acid plays a vital anti-oxidant role in scavenging harmful free radicals in brain cells.[92,93] Furthermore, the levels of ascorbic acid are decreased after a neurological injury such as TBI.[94] Supplementation of ascorbic acid (45 mg/kg or 60 mg/kg) and α-tocopherol (45 mg/kg or 60 mg/kg) demonstrated a reduction in oxidative stress and improved superoxide dismutase activity in rats post-TBI.[95] Another study showed that administration of ascorbic acid (20 mg/kg) alone or in combination with simvastatin (15 mg/

Table 2. Supplementation of vitamins and minerals in preclinical models of traumatic brain injury (TBI)

Vitamins and minerals	Dosage used	Proposed/suggested mechanism	Findings
ATRA (vitamin A metabolite)	10 mg/kg	Anti-inflammatory and anti-apoptotic effects	Brain protective effects but no improvement in neurological and motor deficits in a mouse TBI model
Vitamin B2 (Riboflavin) & Magnesium	7.5 mg/kg (Vitamin B2); 1 mmol/kg (Magnesium)	Anti-oxidant effects	Reduced behavioral impairments, lesion size, edema formation, and expression of GFAP in rat TBI model. Synergistic with Magnesium.
Magnesium sulfate & n-acetyl L tryptophan	30 mg/kg (Magnesium); 2.5 mg/kg (n-acetyl L tryptophan)	Anti-oxidant effects	Reduced BBB permeability and improved functional outcomes in rat TBI model
Vitamin B3 (Nicotinamide)	50 mg/kg, 500 mg/kg or continuous infusion of 12 mg/kg/h with LD of 75 mg/kg	Increased cellular energy as an NAD+ precursor.	Neuroprotective effects and alleviation of behavioral deficits in a rat TBI model. Synergistic with Progesterone.
Vitamin B6 (Pyridoxine)	300 mg/kg or 600 mg/kg	Increased oxygen delivery to damaged tissues.	Alleviation of locomotor behavioral deficits in Rat TBI model. However, only the 600 mg/kg dose showed tissue sparing effect.
Vitamin B9 (Folic acid)	80 µg/kg or 800 µg/kg	Decreased homocysteine levels	(1) Early functional recovery in female TBI piglets treated with 80 µg/kg; (2) No improvement in behavioral outcomes in rats post-TBI treated with 80 µg/kg (low dose) or 800 µg/kg (high dose). Moreover, 800 µg/kg dose worsened neuronal loss
Vitamin B12 (Cobalamin)	0.5 mg/kg or 1.5 mg/kg	Downregulation of the endoplasmic reticulum stress-related apoptosis	Improvement in neurological functional recovery in a mouse TBI model
Vitamin C (Ascorbic Acid) & Vitamin E (α-tocopherol)	45 mg/kg or 60 mg/kg (Vitamin C); 45 mg/kg or 60 mg/kg (Vitamin E)	Improved SOD activity.	Reduction of oxidative stress in rat TBI model.
Vitamin C (Ascorbic Acid) & Simvastatin	20 mg/kg (Ascorbic acid) and 15 mg/kg (Simvastatin)	Diminished vascular inflammatory response	Combination treatment with ascorbic acid and simvastatin improved neurological recovery in a rat TBI model
Vitamin D & Progesterone	1 µg/kg (Vitamin D) and 16 mg/kg (Progesterone)	Anti-inflammatory effects.	Reduced markers of inflammation and neuronal cell death were observed in the rat TBI model. Synergistic with progesterone.
Vitamin E (α-tocopherol)	500 IU/kg	Involvement of BDNF and Sir2.	Improved cognition scores in a mouse TBI model.
Vitamin E (α-tocopherol)	2 IU/g chow diet	Reduction in lipid peroxidation	Decreased amyloidosis and improved memory impairment in Alzheimer's disease mouse post-TBI
Zinc	180 ppm	Attenuation of redox signaling.	Reduced neuropsychiatric symptoms in rat TBI model.
Selenium	1.5 mg/kg	Anti-oxidant effect	Reduction in lipid peroxidation in a rat TBI model
Melatonin	5 mg/kg	Attenuation of oxidative stress	Reduction in lipid peroxidation in a rat TBI model

ATRA, all-trans retinoic acid; BBB, blood-brain barrier; BNDF, brain-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; NAD+; Sir2, silent information regulator 2; SOD, superoxide dismutase; TBI, traumatic brain injury.

kg) in rats post-TBI significantly attenuated brain endothelial inflammation and improved neurological recovery (ascorbic acid and simvastatin alone) respectively.[96]

Vitamin D

Research data examining the independent use of vitamin D supplementation for treating TBI is lacking. However, vitamin D is a promising substance used as a neuroprotective adjuvant in post-TBI progesterone therapy. Combination treatment of vitamin D (1 µg/kg) and progesterone (16 mg/kg) showed reduced markers of inflammation and neuronal cell death in a rat TBI model.[97] Interestingly, vitamin D deficiency deteriorates TBI outcomes and attenuates the protective benefits of progesterone after TBI in rats. These findings were reversed with vitamin D supplementation.[98] Ongoing randomized placebo-controlled clinical trial examining the effects of high and low-dose vitamin D supplementation on in-

Table 3. Dietary supplement uses in clinical and preclinical models of traumatic brain injury (TBI)

Dietary supplements	Dosage used	Proposed/suggested mechanism	Findings
Creatine	400 mg/kg	Increased phosphocreatine levels and ATP-buffering capability.	Reduction of headache frequency, fatigue, and dizziness in a pilot study of 39 adolescents post-TBI. Up to 50% reduction of cortical damage in rat TBI model.
DHA	10 mg/kg/d or 40 mg/kg/d	Increase in anti-oxidant capacity molecules, including SOD and Sir2.	Decreased axonal injury and apoptotic markers in rat TBI model.
Curcumin	500 ppm	Involvement of BDNF.	Reduction in oxidative stress, conserved synaptic plasticity, and cognitive function in rat TBI model.
Resveratrol	100 mg/kg	(1) Action via heme oxygenase-1; (2) Suppression of the NLRP3 inflammasome	Reduced neuroinflammation and secondary brain injury in mice mTBI model.
Enzogenol	1,000 mg/d	Anti-inflammatory and anti-oxidant effects	Improved cognitive function in a phase II RCT in patients treated for mild TBI.
Sulforaphane	5 mg/kg	Induction of Nrf2-driven genes	Reduced cerebral edema and BBB permeability in rat TBI model. Working memory also improved.
Ginseng	20–80 mg/kg	(1) Increased expression of NGF, GDNF, NCAM, and BrdU/nestin neural stem cells; (2) Decreased apoptotic cell death, downregulation of inflammatory cytokines, upregulation of anti-inflammatory interleukin-10, and increased SOD activity	Improved recovery of neurological function and reduced neuronal cell loss in rat TBI model.
Astaxanthin	25 mg/kg or 75 mg/kg	Increased BDNF, GAP-43, and SYP expression	Neuroprotection improved sensorimotor and enhanced cognitive function in a mouse TBI model
Melatonin	5 mg/kg	Attenuation of oxidative stress	Reduction in lipid peroxidation in a rat TBI model
	(1) 150 mg/kg (rat study); (2) 4 g loading dose followed by 4 g for four days and 3 g for three days (human study)	Attenuation of oxidative stress	(1) Reduction in lipid peroxidation in a rat TBI model; (2) Resolution of early sequelae of blast-induced mTBI
Pycnogenol	150 mg/kg	Attenuation of oxidative stress	Ameliorated oxidative stress, synaptic protein loss, and inflammatory cytokines in a rat TBI model

BBB, blood-brain barrier; BNDF, brain-derived neurotrophic factor; BrdU, Bromodeoxyuridine; DHA, docosahexaenoic Acid; GDNF, glial cell line-derived neurotrophic factor; NGF, nerve growth factor; NCAM, neuronal cell adhesion molecule; NSC, neural stem cell; NLRP3, nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3; Nrf2, nuclear factor erythroid 2-related factor 2; RCT; randomized controlled trial; Sir2, silent information regulator 2; SOD, superoxide dismutase; TBI, traumatic brain injury.

flammatory cytokines, clinical outcomes, and mortality in patients with severe TBI will further elucidate the role of vitamin D in TBI recovery.[99]

Vitamin E

Treatment with vitamin E attenuates cellular repair following tissue injury.[100] Moreover, vitamin E protects cells from free radicals due to its anti-oxidant properties.[101] Supplementation of vitamin E (500 IU/kg) for four weeks demonstrated improved cognition scores in a mice TBI model. These effects are credited to vitamin E's role in increasing the brain levels of brain-derived neurotrophic factor (BNDF) and silent information regulator 2 (Sir2).[102] Other studies have suggested that vitamin E supplementation post-TBI is neuroprotective via the reduction of lipid peroxidation.[103,104]

Zinc and selenium

Zinc supplementation post-TBI is controversial. While some studies have suggested that zinc levels increase following brain injury, others have suggested that zinc levels decrease.[67,105–107] Despite this discrepancy, zinc supplementation studies have shown promising results in preclinical models of TBI. Zinc supplementation (180 ppm) in rats demonstrated behavioral resiliency to TBI-induced neuropsychiatric symptoms of depression and anxiety.[108] The mechanism through zinc's neuroprotective effects in TBI is

still uncertain. However, one study suggested that zinc may affect redox signaling directly.[109] Selenium is another mineral shown to have a neuroprotective effect in rats post-TBI.[110] However, clinical trials examining the impact of early selenium administration post-TBI have shown mixed results.[111,112]

Dietary supplements

Creatine

Creatine supplementation increases phosphocreatine levels in the brain, thereby providing adenosine triphosphate (ATP)-buffering capability in TBI-induced hypoxia and cortical blood flow reduction.[113–115] Six months of creatine supplementation, given at doses of 400 mg/kg of body weight, correlated with a decrease in TBI symptoms such as frequency of headaches, fatigue, and dizziness in a cohort of 39 adolescents.[116] Additionally, Sullivan *et al*. showed that rats fed with 1% creatine-enriched diet four weeks prior to TBI initiation showed a 50% reduction in cortical damage.[117]

Docosahexaenoic acid (DHA)

Studies suggest that DHA may play a role in mitigating the cognitive dysfunction seen post-TBI.[5] Wu *et al*. showed that DHA chow supplementation significantly increased DHA content in the brain of post-TBI rats and lessened cognitive decay associated with TBI. Possible mechanisms revolve around preserving membrane integrity *via* an increase in anti-oxidant capacity molecules superoxide dismutase (SOD) and Sir2.[118] In another study, 30 days of prophylactic supplementation of DHA (10 mg/kg/d or 40 mg/kg/d) in rats post-TBI showed a reduction in injured axons and decreased apoptotic markers.[119] In general, dosages of 1 to 7.5 g/d have been demonstrated as being safe for human consumption.[120]

Curcumin

Curcumin is the primary bioactive substance found in turmeric and has been associated with anti-inflammatory properties. In a TBI rat model, curcumin (500 ppm) given for four weeks prior to injury mitigated TBI-associated oxidative stress, conserved synaptic plasticity, and improved behavioral outcomes via normalization.[121]

Resveratrol

In a mild TBI mouse model, resveratrol supplementation (100 mg/kg) demonstrated reduced neuroinflammation and secondary brain injury.[122,123] Resveratrol is thought to act *via* the neuroprotective and anti-oxidant properties of heme oxygenase-1 and has shown synergistic properties with melatonin.[124] Additionally, resveratrol has been shown to have a neuroprotective effect post-TBI via suppression of the nucleotide-binding domain, leucine-rich-containing family, and pyrin domain-containing-3 (NLRP3) inflammasome.[123]

Enzogenol

Enzogenol is a flavonoid-rich extract known for its anti-oxidant and anti-inflammatory properties.[125] Class 2B evidence has demonstrated that enzogenol supplementation (1,000 mg/day) may improve cognitive function in patients with mild TBI.[126]

Sulforaphane

Commonly found in cruciferous vegetables, sulforaphane (5mg/kg) attenuated blood-brain-barrier permeability, reduced cerebral edema, and improved working memory in rats following TBI. Sulforaphane's beneficial effects were linked to the induction of cytoprotective, nuclear factor erythroid 2-related factor 2(Nrf2)-driven genes and associated protein products.[127]

Ginseng

Ginseng is a traditional Chinese herb with a bioactive component, saponins, that have been linked with reducing inflammation.[128] Rats who received ginseng saponins (20–80 mg/kg) following TBI demonstrated improved recovery of neurological function and reduced neuronal cell loss. These effects were associated with an increased expression of nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and neuronal cell adhesion molecule (NCAM), inhibited expression of neurite outgrowth inhibitor- A, B (Nogo-A and Nogo-B), tenascin-C (TN-C), increased number of Bromodeoxyuridine (BrdU)/nestin-positive neural stem cells (NSC), decreased apoptotic cell death, downregulation of inflammatory cytokines, upregulation of anti-inflammatory interleukin-10, and increased SOD activity.[129,130]

Miscellaneous supplements

Astaxanthin is a carotenoid and an anti-oxidant. Astaxanthin (25 mg/kg or 75 mg/kg) has been shown to reduce lesion size, decrease neuronal loss, and improve sensorimotor and cognitive recovery in a mouse TBI model.[131] Additionally, melatonin (5 mg/kg) and N-Acetylcysteine (150 mg/kg) administration post-TBI has also been shown to be neuroprotective *via* attenuation of oxidative stress.[110,132] In a double-blind, placebo-controlled RCT blast TBI study, N-Acetylcysteine (4 g loading dose followed by 4 g for four days and 3 g for three days) was shown to significantly mitigate blast-induced mild TBI symptoms that include dizziness, confusion, hearing loss, headache, impaired memory, and sleep disturbances by day seven post-TBI compared to placebo.[133] Pycnogenol (PYC), a powerful natural anti-oxidant, has anti-inflammatory and anti-oxidative stress effects that may be protective in many neuroinflammatory conditions.[134–138] An ongoing double-blind, placebo-controlled RCT aims to address the neuroprotective effects of PYC on the clinical, nutritional, and inflammatory status of TBI patients.[139] The findings from the PYC RCT are promising, given that in a rat model of TBI, PYC (150 mg/kg) alleviated oxidative stress, synaptic protein loss, and inflammatory cytokines.[140]

Future Directions

Future studies are needed to examine the long-term impact of adequate nutritional care in adult and pediatric patients with TBI. Most of the vitamin, mineral, and supplement studies discussed in this review were conducted on animal models. RCTs are needed to examine whether the demonstrated potential of the vitamins, minerals, and supplements extrapolate to human TBI. Additionally, given that gastrointestinal dysfunction is apparently post-TBI,

there may be a plausible role for probiotics, prebiotics, and fecal transplantation as tools that mitigate the nutritional deficit seen in many TBI patients.

Conclusion

Nutrition improves outcomes for patients with neurotrauma. This focused review highlights the recommended calorie distribution to maintain energy requirements. This must be maintained even if different routes of administration are utilized. Furthermore, emerging evidence has indicated the importance of vitamins, minerals, and supplements. The field continues to change, but emerging innovation is piloting improvements for overall outcomes following brain injury.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (BL-W), drafting of the manuscript (DCN, JG, ZH, CD, and BL-W), critical revision of the manuscript (DCN and BL-W), and study supervision (BL-W). All authors have contributed significantly to this study and approved the final manuscript.

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