ARTICLE

Nutritional Considerations in the Optometric Management of Mild Traumatic Brain Injury

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ABSTRACT

Mild Traumatic Brain Injury (mTBI) affects a large proportion of the population and the chronic nature of symptoms present a significant socioeconomic challenge to the patient, their families, and to society. Given the multitude of ocular sequelae that may persist in this cohort of patients, eye care professionals play a crucial role in their management. Although further research is warranted, several nutrients and dietary considerations show promising results for mTBI recovery. These include, but are not limited to, omega 3 fatty acids, various dietary antioxidants, creatine, lutein, and zeaxanthin. Many of the nutrients that show beneficial results are prevalent in the Mediterranean Diet. Additionally, current literature shows improvements in cognitive impairment; therefore, this should act as the preferred dietary template for post-TBI patients. Optometric practitioners should strongly consider incorporating nutritional therapies in conjunction with conventional interventions to best improve visual outcomes associated with mTBI.

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INTRODUCTION

Mild traumatic brain injury (mTBI), also known as a concussion, may occur with or without loss of consciousness following an impact to the head and is the most common form of traumatic brain injury (TBI).[1-3] It is estimated that TBI affects more than 10 million people globally each year and represents a major public health challenge among all ages regardless of income level due to post-concussion syndrome (PCS).[4,5] While the majority of cases resolve within 3 months, many symptoms of PCS, which include dizziness, headache, fatigue, irritability, anxiety, insomnia, loss of concentration, loss of memory, ringing in the ears, blurry vision, photophobia, disorientation, confusion and lack of coordination, may persist for up to a year or more.[2,3,6,7] As a significant proportion of mTBI patients are working aged, symptoms that prevent a prompt return to work present a significant burden on the individual, their families, and on the economy as a whole.[8] Although the risk of PCS correlates poorly with the severity of the impact, it can severely affect the quality of life due to ongoing symptoms and disabilities, which may include motor and cognitive impairments as well as mental health effects, such as addiction and mood disorders.[1,8] Given an optometrist's role as a primary health care provider of the visual system, nutritional advice, and dietary intervention may be pertinent management tools in reducing debilitating PCS symptoms.

Pathophysiology of TBI

TBI can be characterized by both a primary injury (occurring at the location of the initial mechanical force to the head) and a secondary injury due to the inflammatory cascade that follows.[4,9,10] The secondary injury may ultimately

lead to cellular apoptosis, diminishing of the blood-brain barrier (BBB) permeability, increased edema, and an intracellular decline in magnesium levels.[4,5] As part of the secondary cascade, glutamate increases to toxic levels, which may induce damage leading to "glutamate excitotoxicity" mediated by increased intracellular calcium levels.[1,2,4,7,9-11] This secondary inflammation results in increased oxidative stress due to significantly elevated levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), both of which damage crucial cellular machinery such as DNA, lipids, and proteins.[4,10]

Post-TBI Visual Dysfunctions

Visual dysfunctions are a common consequence of mTBI and may not present with symptoms immediately due to the delayed onset of secondary inflammation within the nervous system.[12] Ocular health professionals may experience some degree of uncertainty as to the somewhat unique visual symptoms associated with PCS after confirming that visual acuities, visual fields, and the examination of ocular structures reveal no pathology. However, when one considers that approximately 40% of the human brain is primarily devoted to processing vision,[12] it is not entirely surprising that the inflammatory process following a mTBI causes a disruption to the visual system that may present with atypical symptoms. For example, photophobia and increased sensitivity to glare are common among patients with mTBI.[13] As accommodation, vergences, saccades, orbital sensation, eyelid function, visual fields, visual acuities, colour perception, and pupillary function are subserved by 7 of the 12 cranial nerves,[12] it becomes evident that a thorough and comprehensive eye examination with an emphasis on binocular visual function is imperative for patients with a history of mTBI. Dictated by the location of trauma and subsequent inflammation, a variety of ocular sequelae may result. For example, it is estimated that accommodative dysfunctions (of either amplitude or facility) are present in 20-50% of mTBI patients, while vergence dysfunctions are present in about 45-50% of mTBI patients.[12,14] Oculomotor dysfunction (abnormal fixations, pursuits, and saccades) is estimated to be present in about 20% of mTBI patients.[14] Visual midline shift syndrome (VMSS) is defined as a sense of shifted ego centeregocenter, resulting in a lateral lean, drift left or right when walking, or a postural tilt forward or backward (anterior/posterior) and is another diagnosis associated with mTBI.[12,14] Optometric management aims to guide therapeutic improvements in the function of the binocular system, which may involve a combination of therapeutic eyewear (tinted lenses, the use of a prism, etc) and active rehabilitative vision therapy. For the practitioner with a special interest in managing this patient population, dietary considerations may be especially relevant to further improve patient outcomes.

Post-TBI Nutritional Considerations

Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids (PUFA) abundant throughout the human brain and retina that are essential for maintaining membrane fluidity.[15] Three forms of omega-3 fatty acids are utilized by humans: eicosatetraenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA). While ALA is obtained from plant oils, both EPA and DHA are primarily obtained from marine oils.[16] The majority of omega-3 fatty acids in the brain are DHA, which has been shown to decline in TBI animal models.[16,17] EPA and DHA supplementation has shown promise in animal TBI models by demonstrating a reduction in both apoptosis and oxidative stress markers, while promoting cell survival and synaptic plasticity.[18,19] Additionally, DHA supplementation alone has been shown to be effective in counteracting glutamate excitotoxicity as well as in restoring levels of brain-derived neurotrophic factor (BDNF), a crucial protein known to decrease following a TBI that mediates

the survival, growth, and maintenance of neurological cells.[7,17] An even larger effect on the restoration of BDNF was observed when DHA supplementation w as combined with exercise, which is known to regulate enzymes associated with PUFA metabolism, thereby regulating DHA content in the brain.[17] In addition, DHA and exercise showed significant benefits in improving cognitive function, enhancing membrane homeostasis, and in reducing oxidative stress markers in post-TBI animal models.[17] Given these encouraging findings, further research in humans is warranted to determine whether dietary intake of DHA and exercise may reduce the deleterious chronic effects of mTBI on neuronal plasticity and cognitive function. Based on the current available literature, it is hypothesized that omega-3 fatty acid intake (with an emphasis on high DHA content) and regular exercise (as tolerated based on careful management of symptoms) are an important part of long-term mTBI recovery.

Dietary Antioxidants: Ascorbic Acid, Curcumin, Resveratrol & Sulforaphane

Antioxidants are substances that are primarily obtained from dietary sources and may be divided into two categories: enzymes and low-molecular-weight antioxidants.[10] Low-molecular-weight antioxidants may be further subdivided into both hydrophilic, or water-soluble, nutrients (examples include N-acetyl-cysteine, ascorbic acid, and flavonoids) and hydrophobic, or fat-soluble, nutrients (omega-3 fatty acids, carotenoids, resveratrol, etc), most of which are dependent upon dietary intake as they are not synthesized in mammals.[4]

Ascorbic Acid

Ascorbic acid (AA), commonly known as vitamin C, is one of the most abundant water-soluble antioxidants in mammalian tissue but is not synthesized in humans. Although AA is one of the most studied antioxidants and has been shown to decrease post-TBI, a surprisingly limited amount of research has been done to date on its effectiveness in humans post-TBI.[20] One preclinical study demonstrated a clear benefit to AA administration in rats (alone and when combined with Vitamin E), significantly reducing mortality levels and restoring diminished AA levels in the brain.[20] The only known human trial demonstrated a modest benefit in the administration of high-dose AA in TBI patients, showing the decreased progression of perilesional edema on CT scan.[4] Current available research clearly highlights the potential benefit and need for additional studies on vitamin C intake and recovery from mTBI.

Curcumin

Turmeric, the primary source of the polyphenol curcumin, is a spice which has received much attention from the medical/scientific community due to its antioxidant and anti-inflammatory properties.[21] The bioavailability of curcumin supplementation alone may be significantly compromised due to poor absorption, rapid metabolism, and rapid elimination.[21] However, when combined with piperine (the major constituent in black pepper), the bioavailability increases as much as 2000%.[21] Although it has not directly been studied in humans for mTBI outcomes, animal models have shown multiple benefits to improving membrane homeostasis, neuronal signaling, cognitive defects, BDNF levels, motor, and learning performance when administered following TBI.[7,22] In human studies, curcumin has demonstrated a conclusively positive effect on counteracting oxidative stress via several mechanisms including free radical scavenging, modulating the action of glutathione (GSH), and inhibiting ROS-generating enzymes.[21] Curcumin may be particularly helpful in mTBI recovery given its long-established safety profile and relatively low cost, although more targeted research in this patient population would be of benefit in providing improved guidelines on specific dosage recommendations.

Resveratrol

Resveratrol (3,5,4'-trihydroxystilbene) is a natural, dietary phenol and phytoalexin found in grapes, various berries, and peanuts.[23,24] Its benefits in the human diet have garnered interest due to its inherent antioxidant properties, appearing to modulate several cell functions, including defense mechanisms, mitochondrial functions, and inflammatory processes.[4] In animal studies following TBI, resveratrol has been shown to counteract oxidative damage and mitigate the depletion of GSH.[10] Additionally, resveratrol reduced apoptosis and autophagy in TBI models in vitro and in vivo via suppression of reactive oxygen species generation and glycogen synthase kinase 3 beta (GSK-3β) activation.[23] A reduction in harmful lipid peroxidation and glutamate excitotoxicity has also been observed in experimental animal models.[7] Due to these effects, resveratrol may show promise as a therapeutic agent in mTBI patients, though more human trials are needed regarding the overall safety and efficacy of supplementation.

Sulforaphane

Sulforaphane (1-isothiocyanateisothiocyanato-4-methylsulfinyl-butane) is an isothiocyanate antioxidant that has been shown to exhibit anti-inflammatory properties in humans.[25] The principal source of sulforaphane in the human diet is cruciferous vegetables.[26] Examples of cruciferous vegetables include broccoli, cauliflower, brussels sprouts, kale and cabbage. Like other flavonoids, it principally acts on nuclear factor erythroid 2-related factor 2 (NRF2), which is an important transcription factor responsible for regulating the expression of cytoprotective antioxidants and enzymes.[26] NRF2 is sequestered in the cytoplasm and, once activated, helps to scavenge free radicals and promote detoxification within the cell.[10,26] In TBI animal models, sulforaphane administration has been shown to reduce cognitive defects via a reduction in cerebral edema, oxidative stress, and an attenuation of blood-brain-barrier permeability.[26] Although there is insufficient data to conclude supplementation would be beneficial in human mTBI patients, these findings are very supportive of recommending regular consumption of a variety of cruciferous vegetables in the diet.

Creatine

Creatine is an endogenously produced substance in humans, which has traditionally been studied for its positive effects on athletic performance. It is naturally produced by the liver, pancreas, and kidneys of vertebrates from the amino acids arginine, methionine, and glycine.[27-29] Stored in skeletal muscle as free creatine or phosphocreatine, these molecules act as a major energy source for the host.[27] In recent years, interest has arisen regarding creatine as a neuroprotective mediator in a variety of neurological conditions such as Huntington's disease, amyotrophic lateral sclerosis (ALS), cerebral ischemia, Parkinson's disease, and TBI.[29,30] Creatine may be an especially promising therapy given its relative affordability as well as the favorable short-term (35 days at a dosage of 5g/day) safety profile, which has been sufficiently evidenced throughout the literature.[29-32] Both animal and human studies have demonstrated a significant benefit with creatine supplementation in TBI. Rats fed a creatine-enriched diet for 7 days post-TBI had significantly smaller cortical lesions (mitigating cortical damage by 36-50%) compared to control by decreasing intramitochondrial Ca2+ and ROS, yet maintaining the same ATP levels.[33] In human TBI patients under 19 years old, 0.4g/kg of creatine supplementation yielded statistically significant improvements over control subjects in overall cognition, personality/behavior, self-care, and communication scores.[34] At a 6 month follow up of the same subjects, this treatment resulted in a statistically significant improvement in headaches, dizziness, and fatigue.[28] In further support of the above studies, a recent systematic review concluded that creatine may

improve short-term memory and intelligence/reasoning, and that based on current evidence this effect may be more pronounced in diseased, elderly, or stressed individuals who supplement with creatine as opposed to young, healthy individuals.[31] Creatine supplementation may therefore be especially pertinent to patients suffering from chronic mTBI symptoms.

Magnesium

Magnesium is an essential cofactor in over 300 enzymatic reactions and is involved in cellular energy metabolism, protein synthesis, cardiovascular health, regulation of blood glucose, and nervous system function.[35,36] Magnesium supplementation has been widely speculated to be of benefit to brain injured patients as TBI results in an estimated 40-60% decrease in intracellular free magnesium and a 10-15% decrease in total tissue magnesium.[5] Additionally, confirmed deficits in magnesium concentration following TBI have been linked to poorer neurological outcomes.[5] Magnesium plays a crucial role in the brain by inhibiting excitatory glutamate via the N-methyl-D-aspartate (NMDA) receptor where it regulates Ca2+ entry into the postsynaptic neuron.[3,35,36] The known decline in magnesium during the secondary inflammatory process helps to explain the increased Ca2+ mediated glutamate excitotoxicity that occurs. However, despite promising experimental studies, magnesium has yet to be proven as a clinically effective treatment in mTBI.[5] This may be because, contrary to animal studies demonstrating adequate absorption of magnesium across the blood brain barrier (BBB), human trials have conversely shown low bioavailability of parenterally administered magnesium in the cerebrospinal fluid (CSF).[3] Moreover, systematic reviews on the effects of magnesium sulfate administration on patients with TBI demonstrated mixed results with no benefit on mortality rates and only a mild benefit on the functional and quality of life Glasgow Outcome Scale (GOS).[36,37] Although magnesium remains a great management tool, in theory, the fact that current literature suggests translation to humans is currently ineffective may be somewhat discouraging. Despite additional magnesium showing no benefit in this population, deficiency (not uncommon in the Western world general population) has been associated with a variety of diseases, and neurological symptoms have been shown to be more pronounced in magnesium deficient patients.[38] Early signs of magnesium deficiency include loss of appetite, lethargy, nausea, vomiting, fatigue, and weakness, many of which may be similar to the long-term symptoms experienced by TBI patients.[38] Ensuring adequate levels of magnesium through diet and supplementation (if necessary) is important to consider when it comes to nutritional guidance of mTBI patients.

Glutathione

Glutathione is one of the few low molecular weight antioxidants that humans synthesize, playing a crucial role in detoxification, and in scavenging ROS and RNS in times of oxidative stress.[4] Glutathione exists in cells in 2 states: reduced (GSH) and oxidized (GSSG).[39] The ratio of GSH to GSSG determines the redox status of the cell. Healthy cells at rest have a GSH/GSSG ratio >1:100 while the ratio drops to 1:10 in cells exposed to oxidant stress.[39] As decreased glutathione levels (as well as corresponding cysteine and glycine) have been demonstrated post-TBI, the benefits of increasing GSH have been of particular interest.[4,8] While oral administration of glutathione remains controversial (the majority of research showing that oral glutathione does not subsequently increase red blood cell (RBC) glutathione), supplemental cysteine in the form of whey or N-acetylcysteine (NAC) is known to be effective at raising levels of glutathione.[39] N-acetyl-cysteine is an antioxidant precursor to GSH, while N-acetyl-cysteine amide (NACA) represents the amide form of NAC.[9,40] NACA has been researched more recently as its BBB, cellular,

and mitochondrial permeability is higher than that of NAC, resulting in increased central nervous system (CNS) bioavailability.[8,11] As hypothesized, encouraging preclinical research in NACA treated rats has demonstrated increased cortical sparing and functional outcomes following TBI, while decreasing oxidative damage via maintenance of mitochondrial glutathione levels.[9] Given these findings, further research is warranted in the mTBI population, as NACA has yet to be studied in humans. However, when assessing the currently available literature regarding glutathione levels and mTBI, dietary efforts to raise GSH levels during the recovery period appear to be pertinent to improving patient outcomes.

Lutein and Zeaxanthin

Lutein (L) and zeaxanthin (Z) are two plant-derived xanthophyll carotenoids found in human tissue that play a crucial role in ocular and neurological function.[41,42] They represent two of the three carotenoids (the third being meso-zeaxanthin (MZ) found in the human macula in a 1:1:1 ratio where they are collectively referred to as macular pigment (MP).[42,43] Due to their abundance in the macula, both L and Z have garnered significant attention regarding their role in slowing the progression of age-related macular degeneration (AMD). In addition to their known positive effects on ocular tissue, there has been significant interest in their neurological benefits given the fact that these two antioxidants alone account for an estimated two thirds of the total carotenoid concentration in the brain.[44] Of particular relevance to PCS patients suffering with chronic symptoms of photophobia, supplementation of lutein (10mg/day) and zeaxanthin (2mg/day) in young, healthy human subjects demonstrated statistically significant improvements in chromatic contrast sensitivity as well as overall recovery from photo stress (defined as the time to recover sight following a temporary light-induced loss of sight as a result of bleaching).[41] In addition to speeding up photo stress recovery, supplementation showed a reduction in the effects of glare disability, extending the visual range and improving chromatic contrast.[41,42] An older patient population (mean age of 72 years old) studied for neurological effects (also supplementing 10+2mg/day of L+Z, respectively), showed enhanced cerebral perfusion on functional magnetic resonance imaging (fMRI) resulting in improved cognitive function on a verbal learning task.[45] Interestingly, the addition of MZ to L+Z supplementation may confer further benefit regarding visual performance, as was demonstrated by optimizing MP and contrast sensitivity in early AMD patients.[45,46] Given the current evidence on carotenoid supplementation, there may be a disproportionate benefit to cognition in adult patients with existing cognitive decline or impairment.[47] Being fat-soluble nutrients that are primarilyobtained through fruit and vegetable consumption, and given that they readily cross the BBB,[44] lutein and zeaxanthin intake (via dietary sources and/or supplementation) appear to be key nutrients for optimal visual and neurological function.

DISCUSSION

Given the prevalence and chronic visual symptoms that persist following mTBI, several of the outlined nutrients may be of significant benefit to the optometric practitioner, especially when combined with other known optometric therapies (therapeutic eyewear, vision therapy, etc). Given the quality of human evidence and well-established safety profiles of both creatine monohydrate and carotenoid supplementation, these may be particularly beneficial to patients as part of a supplement protocol. Despite added magnesium showing no additional benefit in human trials, emphasis should be placed on the importance of obtaining adequate amounts of this crucial nutrient via diet or supplementation, if required, to prevent deficiency. Omega-3 fatty acids, dietary antioxidants, and nutrients which promote GSH production all show encouraging results in improving the chronic effects of TBI in animal models. However, further human

supplementation trials are warranted to establish more robust safety and efficacy profiles for these modalities. When considering top dietary sources of these nutrients, practitioners should be aware of dietary patterns that are known to promote overall health and specifically maximize EPA, DHA, ascorbic acid, curcumin, resveratrol, sulforaphane, cysteine, glutamine, and glycine (GSH precursors) intake. The Mediterranean Diet (MD), defined as a dietary pattern rich in antioxidant compounds and bioactive elements with anti-inflammatory effects that have a low glycemic index[48] may be the most relevant dietary template in the mTBI population. High quality evidence has shown that encouraging eating patterns with liberal amounts of olive oil (high monounsaturated/saturated fat ratio), fruits, vegetables, nuts, legumes, and fish (at least 3 times per week) while favoring poultry intake over red meat, moderately consuming wine, and restricting red and processed meat, dairy, carbonated/sugared beverages, cakes, and highly processed grains can reduce the risk of many chronic diseases and cognitive impairment.[48]

Using the MD as a dietary template, emphasis in the mTBI population should be placed on consuming liberal amounts of green- and orange-colored vegetables paired with olive oil (lutein and zeaxanthin), cruciferous vegetables (sulforaphane), turmeric with black pepper (curcumin), and smaller, wild fish sources such as salmon, trout, sardines, and mackerel (EPA and DHA). Alcohol consumption is generally not recommended for those suffering from chronic post-TBI symptoms; binge drinking and liquor consumption should be avoided. However, if patients do consume alcohol, moderate red wine consumption with meals should be prioritized due to the potential benefits from its resveratrol content.[48] In conjunction with appropriate optometric therapies, nutritional guidance should be provided to those patients suffering from chronic visual and cognitive PCS symptoms. Although further studies are warranted, these nutritional recommendations may be particularly relevant to those optometric practitioners directly involved in vision therapy and rehabilitation.

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Declaration of Interest

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