Chapter 14
Sports Concussions: Is There a Role for Alternative Treatments?

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Introduction

Around 3.8 million sports-related concussions occur in the United States each year; and up to 50% of those go unreported [1]. Sports-related concussions are commonly referred to as mild traumatic brain injuries (TBI) that affect a wide range of recreational and professional sports athletes. Mild TBIs typically result from biomechanical forces that induce complex cellular metabolic cascades. This impairs neuronal membrane and transmitter function and causes ionic shifts that increase intracellular glutamate and calcium [2]. The resulting transient clinical symptoms often reflect a functional injury from disruption of brain networks, which cannot be depicted grossly with neuroimaging. Despite the complex pathophysiological constellation of neurologic and musculoskeletal symptoms, the majority (80–90%) of sports-related concussive episodes resolve spontaneously in 7–10 days [3].

Traditional treatment has hence involved complete physical and mental rest with low light and low sound stimulating environments until symptom resolution. However, complete rest is better substituted with controlled submaximal activity after 72 hours of injury to hasten recovery [4]. Despite that, the overall

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management paradigms of mild TBIs remains controversial with varying success rates of different therapies. This might be attributed to the lack of general consensus and concrete evidence as well as the absence of Food and Drug Administration (FDA)-approved pharmacological interventions. Thus, physicians often target such symptoms with corticosteroids and anti-inflammatory drugs that inhibit arachidonic acid or modify monoamine function, glutamate receptor antagonists, calcium channel blockers, or thyrotrophin-releasing hormones [5]. Many nonpharmaceutical alternatives such as dietary supplements, vitamins, and minerals have already been utilized in the management of neurodegenerative conditions. These agents have also shown promising results in the management of a wide array of neurologic sequelae resulting from repetitive concussive head injury such as post-concussion syndrome (PCS), prolonged PCS, and post-traumatic stress disorder (PTSD) (Fig. 14.1) [2, 6].

Proper assessment and evaluation remain an integral part in managing concussed patients for optimal delivery of effective care. This includes both onsite tools of assessment and further comprehensive neuropsychological testing. The following chapter discusses the scientific basis of proposed supplements and their potential implications in the treatment of sports concussion and prevention of its short- and long-term sequelae such as PCS.

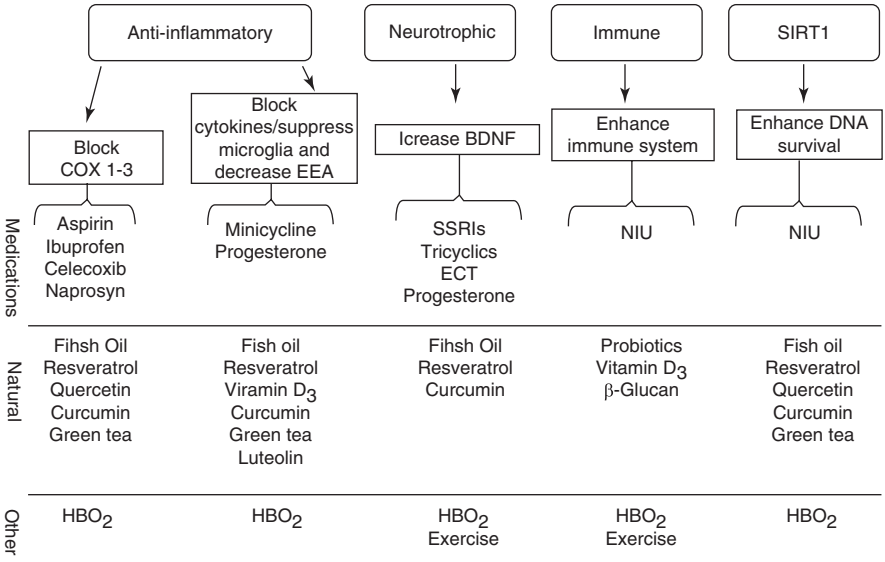

Fig. 14.1 Both pharmacological agents and nonpharmaceutical alternatives target similar pathways responsible for immunoexcitotoxicity post brain injury. Natural alternatives may be as effective without the undesirable side effects associated with their pharmacological counterparts. (Courtesy of Maroon et al. [5])

Abbreviations: BDNF brain-derived neurotrophic factor, COX cyclooxygenase, ECT electroconvulsive therapy, EAA excitatory amino acids, HBO2 hyperbaric oxygen, NIU no pharmacological agents in use, SIRT1 sirtuin 1, SSRI selective serotonin reuptake inhibitor

Supplements

Omega-3-Fatty Acids

Omega-3-Fatty Acids (O3FAs) have been found to have significant health benefits in neurological disease prevention and treatment [7]. O3FAs are among the most popular supplements for the management of concussions partly due to their promising neuroprotective effects in animal experiments [8], and their role as a natural anti-inflammatory [9]. The growing evidence behind their medicinal properties and health benefits have made fish oil capsules and oils, which contain O3FAs, the most common dietary supplement in the United States [10].

Fatty acids comprise the bilipid membrane of every cell in the human body. They are involved in many vital structural roles that enhance neuronal cell fluidity, stability, and neurotransmitter functions [11]. The brain especially comprises mostly fatty acids, of which 40% of those are docosahexaenoic acid (DHA) [12, 13]. DHA, eicosapentaenoic acid (EPA), and α-Linolenic acid are the most important O3FAs with potential benefits in concussion and traumatic brain injury. They are referred to as omega-3 essential fatty acids (EFAs) because of the inability of the human body to endogenously synthesize them and therefore must be obtained from dietary nutrition sources, such as fish, walnuts, flaxseeds, and certain other vegetables. Deficiency in omega-3 EFAs can induce various forms of brain dysfunction and disrupt the normal composition and chemical properties of neuronal cell membranes, neurons, oligodendrocytes, and astrocytes leading to neurosensory and behavioral abnormalities [7, 13].

Animal studies have demonstrated that supplementation of O3FA in rats before sustaining a concussion can preserve learning and protect against reduced neuronal plasticity by normalizing protein levels associated with neuronal circuit function, cognitive processing, synaptic facilitation, neuronal excitability, and locomotor control [14]. When administered 30 days before TBI, they have shown to reduce the response to injury, evident by reduction in markers of cellular injury and apoptosis, axonal counts, and memory as assessed by water-maze testing [15].

Whereas supplementation of O3FAs prior to concussion seems beneficial, studies have also reported that supplementation in animals following TBI helps maintain genomic stability and cellular hemostasis [16], as well as decrease the amount of injury the brain sustains [17]. DHA supplementation significantly reduces the number of swollen, disconnected, and injured axons [11, 18]. The administration of EPA has also shown to attenuate neuronal cell death in rats suffering from an interruption in blood flow following injury [14]. Other studies have described that long-term treatment with EPA improved age-related reduction in blood flow in the brain and increased glucose metabolism [19]. Fish oil has also demonstrated the ability to attenuate TBI-induced deficits and dopamine release in the striatum, which could potentially benefit behavioral impairments [20].

Perhaps the main benefit of omega-3 EFAs lies within their ant-inflammatory properties that can potentially counter brain trauma-related inflammation [14, 18].

They are able to stabilize cell membranes and inhibit the release of pro-inflammatory prostaglandins such as arachidonic acid, a major mediator of the inflammatory response [11, 14, 21]. At the cellular level, cyclooxygenase (COX) enzyme maintains an equilibrium between the conversion of arachidonic acid (AA) from omega-6 EFA into proinflammatory prostaglandin E2 (PGE2) and anti-inflammatory prostaglandin E3 (PGE3) from EPA [10, 22]. As the percentage of EPA increases compared to the amount of AA within the phospholipid membrane of a cell, PGE2 production is downregulated through competitive inhibition and COX favors the anti-inflammatory PGE3 production (Fig. 14.2). Consequently, the inflammatory cascade is blunted, and the synthesis of inflammatory cytokines interleukin (IL)-1, tumor necrosis factor (TNF)-α, IL-6, and IL-8 is decreased [12, 23]. Downstream mediators of nuclear factor (NF)-κB pathway are also inhibited, which restricts chronic microglia activation [24]. While EPA is a precursor for resolvins [25], DHA is a precursor of both resolvins, and protectins synthesis; both of which halt inflammation [26] and possibly limit the damage from concussion.

Researchers have found that O3FAs increase neuronal survival following injury by activating cellular N-methyl-D-aspartate (NMDA) receptors [27], and

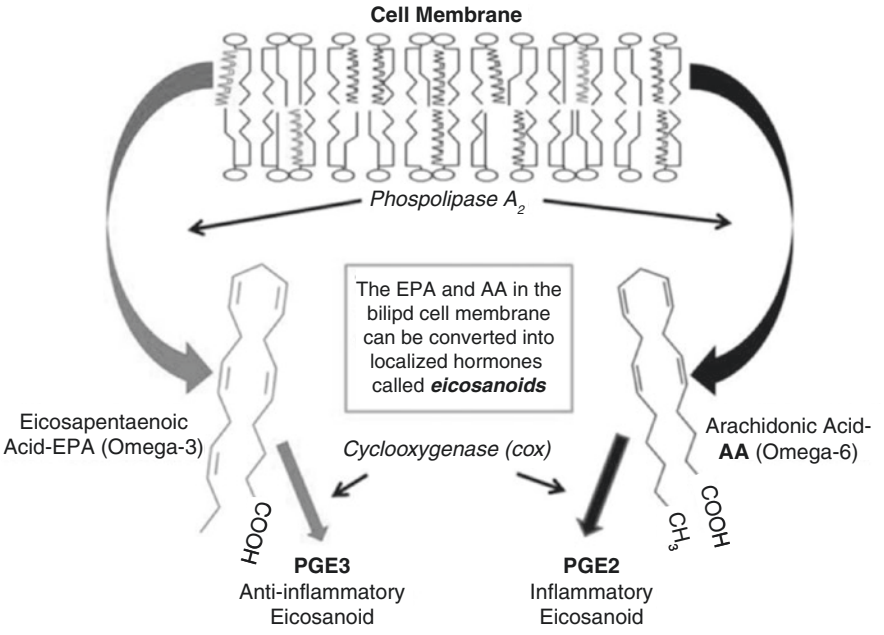

Fig. 14.2 The cell membrane contains various concentrations of both omega-3 EFA and omega-6 EFA. Following trauma or injury, COX enzyme maintains an equilibrium between the conversion of AA from omega-6 EFA into proinflammatory PGE2, and anti-inflammatory PGE3 from EPA. (Courtesy of Maroon et al. [5])

Abbreviations: EFA essential fatty acids, COX cyclooxygenase, AA arachidonic acid, PGE prostaglandin E, EPA eicosapentaenoic acid

suppressing the toxic effects of the excitatory neurotransmitter glutamate, which activates amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors [28], following TBI. DHA helps attenuate the inhibition of antioxidant enzymes, downregulate nitrous oxide (NO) production, and inhibit intracellular Ca^{2+} influx and subsequent neuronal death following brain injury [11, 14, 19]. This also promotes neurogenesis through neuronal neurotrophic stimulated replication and growth [29]. Additionally, DHA undergoes oxidation following cerebral injury to produce neuroprotectin D1, a counter-proinflammatory messenger. This ultimately downregulates neutrophil infiltration and the expression of inflammatory TNF-α, IL-6, and COX-2 in microglial cells [30]. One study in American football players who received DHA supplementation observed a decrease in neurofilament light (NFL) levels across the football season [31]. NFL levels are known to increase to up to 400% after repetitive head trauma [32].

Adequate supplementation of omega-3 EFA has indeed shown to improve a wide range of brain-related conditions with a common underlying inflammatory cascade; which include PCS and chronic traumatic encephalopathy (CTE). They can supply the brain with the needed fatty acids for healing and reduce neurologic inflammation and its undesired complications.

The suggested dosing is a total of 1.5–5.0 g of approximately equal parts of EPA and DHA fish oil per day for the improvement of concussion symptoms [5, 31]. Omega-3 fish oils are readily available, highly safe, and well tolerated but should be used with caution in those on prescription anticoagulants because of their potential to increase bleeding [13]. Dosing requirements for those on other prescription medications or with underlying diseases should also be adjusted. Common side effects include belching, heartburn, bad breath, nausea, and loose stools.

Resveratrol

Resveratrol is a naturally occurring polyphenol found in many different plant sources. Polyphenols protect plants from microbial infections and excessive ultraviolet radiation [33]; and provide much of the nutritional benefits behind the consumption of fruits and vegetables. This entails significant anticancer, anti-inflammatory, antioxidant, and DNA-protective actions [34]. Resveratrol was discovered in 1940, and has since gained popularity due the aforementioned properties, and its ability to increase insulin sensitivity in both animals and humans [35]. Its consumption has also cleared β-amyloid and reduced the risk of Alzheimer's disease in population studies [36]. More importantly, resveratrol crosses the blood brain barrier (BBB) and possesses much of the neuroprotective effects and anti-inflammatory properties seen with O3FA supplementation. This includes the suppression of proinflammatory PGE2 synthesis, downregulation of TNF-α- and IL-1β-induced NF-κB and microglial activation [33, 37].

Following neurologic injury, free radicals induce lipid peroxidation of arachidonic acid in neuronal cell membranes [38]. This then leads to the formation of

neurotoxic aldehydes that inhibit cellular protein function. Resveratrol contains multiple phenolic hydroxyl groups [38], which allow it to donate electrons and neutralize the superoxide and lipid peroxyl radicals produced following injury [39]. In animals, resveratrol is also able to attenuate glutamate release and ecotoxicity [40], reduce neutrophil infiltration, and improve Na^+/K^+-ATPase activity following TBI [21].

Researchers at the University of Pittsburgh found that administrating 100 mg/kg of resveratrol to rats after controlled brain injury, provided neuroprotective effects in the form of motor performance and visuospatial memory [21]. Other animal studies demonstrated reduced oxidative stress, neuronal loss, and lesion volume as well as improved behavioral measures of locomotion, anxiety, and memory [41]. Furthermore, resveratrol supplementation has been found to increase cerebral blood flow [42] and at higher doses extend animal life span [43], slow the development of chronic neurodegenerative disease, and improve patient outcomes following stroke, global cerebral ischemia, spinal cord injury, and TBI [44, 45].

Resveratrol is found in multiple natural dietary sources, including peanuts and chocolate, but is most concentrated in the plant *Polygonum cuspidatum* (Japanese knotweed) and the skins of red wine grapes [34, 37]. It is also commercially available in its bioactive trans- form as a dietary supplement [33]. The typical suggested supplement dose is between 50 to 500 mg/day. It is generally safe with no significant reported side effects; however, patients taking antiplatelet- or coagulation-altering products should be cautioned about the observed antiplatelet effects of resveratrol [33].

Vitamin D3

Vitamin D is one of the fat-soluble vitamins known for physiologic calcium homeostasis and bone health. Its active form, vitamin D3, is produced in the skin by ultraviolet B radiation from the sun and is involved in a number of cellular and tissue functions. It impacts immunity, inflammation, cardiovascular health as well as neuronal regulation [46, 47].

Vitamin D's cholesterol backbone allows it to easily traverse neural cell membranes in the brain where it is commonly referred to as vitamin D hormone (VDH). VDH functions as a neurosteroid and binds to nuclear vitamin D receptors to modulate neuronal gene transcription. Vitamin D deficiency increases inflammatory damage and behavioral impairment following experimental head injury [18]. When supplemented following TBI, VDH has been shown to reduce inflammation, necrosis, apoptosis, and cerebral edema [48], especially when administered with progesterone [49]. Patients supplemented with both Vitamin D3 and progesterone experienced better recovery rates following severe TBI [48]; the combination is thought to induce reductions in astrocyte activation and NF-kB phosphorylation [50].

In general, VDH is known to inhibit the upregulation of the proinflammatory cytokines IL-6, IL-17, TNF-α, and IFN-γ by inhibiting NF-κB [51] and increasing IL-10 levels; the anti-inflammatory cytokine known to be lower in the brains of patients with Alzheimer's disease [52]. However, its neuroprotective effects specifically are thought to be due to decreased glutamate-induced neuronal cell death [49] and downregulation of L-type calcium channels expression in neurons following TBI [53]. This is primarily via increasing phosphorylation, and subsequent activation, of mitogen activated protein kinase (MAPK) [49]. The upregulation of MAPK then induces the expression of antiapoptotic genes such as *Bcl-2*, which protects neurons from toxic injury.

The importance of Vitamin D intake and supplementation extends beyond concussive head injury. Vitamin D deficiency is seasonal and geographical, whereby risk is higher in winter and in southern parts of the United States [54]. It is a significant public health risk in the United States due to the use of sunblock, dark-colored skin, and decreased activity levels [55]. High-risk populations include institutionalized and hospitalized elderly patients as well as up to 30% of athletes [56].

Dietary sources of vitamin D include fatty fish, fish liver oils, fortified milk, cheese, beef, and egg yolks [55]. The current recommended dietary allowance is between 800 and 1000 IU/day, but the replacement dose in deficient athletes appears to lie between 35,000 and 50,000 IU/wk. [57]. Vitamin D supplementation is generally safe and should be tailored to blood levels. Excessive amounts may increase calcium in the blood and risk the development of kidney stones and arterial hardening.

Curcumin

Curcumin is a flavonoid compound found in the Indian spice turmeric; a flowering plant of the ginger family that provides the yellow pigment seen in many curries [58]. Flavonoids have been historically used to treat digestive disorders and promote wound healing [12, 22]. They have gained more popularity recently largely due to their potent anti-inflammatory, antioxidant, and antineoplastic effects [58]. The anti-inflammatory actions of curcumin arise from its ability to suppress messenger RNA (mRNA) production for proinflammatory mediators, activation of Nrf2, and inhibition of NF-κB, COX-1, and COX-2 [59]. This had made it comparable to nonsteroidal anti-inflammatory drugs (NSAIDs) in effect but with a safer side effect profile [5].

Curcumin is neuroprotectant after TBI in animals [38, 60]. It suppresses neuroinflammation, protects the brain from neurotoxins [39], and potentially promotes memory and cognitive function [61]. The polyphenolic derivatives of curcumin prevent post-traumatic perineuronal microgliosis and reactive astrogliosis [62], and promote neuronal survival and synaptic plasticity. They decrease oxidative stress [38, 60] and the edema following TBI and ischemic neurodegeneration by

counteracting post-traumatic upregulation of astrocyte water channel aquaporin-4 [62, 63]. The antiapoptotic function of curcumin is similar to that of vitamin D, and that is by upregulating the expression of *Bcl-2* gene. The administration of curcumin both pre- and post-injury seems beneficial [61]. Yet, the therapeutic window for significant neuroprotection after injury seems to be less than 1 hour and far greater effects were observed when it was supplemented before injury [60].

Curcumin is safe and available for supplementation at nano-sized units for better gastrointestinal absorption. The suggested dosage of supplementation is 400–600 mg taken three times per day [5]. Extended use may cause stomach disturbance and ulcers in rare cases.

Magnesium and Vitamin B2 (Riboflavin)

Magnesium is an essential intracellular cation involved in the stability of polyphosphate compounds cells and a multitude of vital human processes, including protein synthesis, smooth muscle tone, energy metabolism, immune system regulation, and the maintenance of calcium and ionic transmembrane gradients [5]. It has been commonly prescribed as a laxative, antacid, or to correct abnormal nerve excitation or blood vessel spasm owing to its role in mitochondrial membrane stability and coupling of oxidative phosphorylation. More importantly, magnesium decline is thought to play a major role in the neuronal pathogenesis following TBI. Magnesium levels seem to be significantly lower after TBI in both animals and humans; this increases the likelihood of apoptosis by interrupting sufficient energy production during recovery [64]. Its administration attenuates immunoexcitotoxicity, especially in individuals with hypomagnesaemia.

Magnesium regulates the influx of Ca^{2+} in neurons by decreasing glutamate release, and acts as a noncompetitive inhibitor of NMDA receptors [65]. Following a concussion, the decrease in intracellular Mg levels and altered cellular membrane potentials result in transient neurologic dysfunction [64] and neural destruction seen in severe cases. Humans and animals with low cerebrospinal fluid (CSF) or serum magnesium levels experience worse neurological outcomes following ischemia and TBI [66]. The supplementation of magnesium post-injury improves both Glasgow outcome scale and Glasgow coma scale scores, but seems to have no mortality benefit in patients with severe TBI [67].

Magnesium similarly decreases edema and lesion size in animals by downregulating the transcription of aquaporin-4 channels [68]. The administration of magnesium has similarly improved functional outcomes in stroke patients and reduced the risk of cerebral palsy in preterm births [69]. Low cytosolic levels of magnesium have also been linked to the pathogenesis of migraine and cluster headaches as well as to the precipitation of seizures [70]. It may therefore have implications in post-concussion recovery period and post-traumatic seizures.

Vitamin B2 (Riboflavin) is a co-factor in oxidative metabolism and seems to also have therapeutic potential in the treatment of human TBI. Riboflavin administration

following traumatic frontal cortex contusion in animals reduced lesion volume, edema formation, and expression of glial fibrillary acidic protein (GFAP), as well as significantly improved behavioral outcomes [71]. The combination of Mg chloride and riboflavin seems to have a synergistic effect therapeutically as their administration together in one animal study improved functional recovery to a greater extent when administered shortly after frontal cortical contusion injury [72]. Their combination may also reduce the frequency and severity of post-traumatic migraine headaches [73]. A randomized clinical trial of Mg, riboflavin, and Q10 supplementation demonstrated significantly reduced symptom severity migraine attacks [74].

More than 60% of Americans aged >20 years as well as the majority of athletes receive inadequate amounts of magnesium [75]. Magnesium is found naturally in nuts, whole grains, legumes, and vegetables, as well as in over-the-counter supplements with the recommended dosage being between 80 and 420 mg/day, depending on age and sex of the patient [76]. Apart from minor gastrointestinal side effects, patients on calcium channel blockers for high blood pressure, for example, should exercise caution due to the possibility of excessively low blood pressure drop when combined with magnesium [76].

N-Acetyl Cysteine

N-acetyl cysteine (NAC) is an acetyl derivative of the amino acid cysteine and is among the few supplements to have shown promising data in clinical trials. It is commonly used as an antidote for acetaminophen overdose and toxicity and has also shown to reduce recovery times in military blast mild TBI, when supplemented within 24 hours of injury [77]. In animal studies, its supplementation after TBI showed significant behavioral recovery when administered alone and in combination with minocycline or selenium [77]. NAC is safe, well-tolerated, and widely available over the counter, but physicians and patients should take note of its interaction with nitroglycerin causing vasodilation [78]. Mild side effects include nausea, vomiting, and gastrointestinal upset [78]. No recommended dose has been suggested and further studies are needed to elucidate its antioxidant properties in sports concussions.

Vitamins E and C

The supplementation of vitamins E and C have been studied in both animals and humans following concussive injuries. Ascorbic acid (vitamin C) is a water-soluble free radical scavenger that helps transform vitamin E to its active form; a lipid-soluble lipid peroxidation inhibitor present in high concentrations in the brain [61]. The inhibition of lipid peroxidation has been linked to neuroprotective effects following TBIs [38]. While the supplementation of vitamin E in rats post-concussion

minimized functional neurologic deficits and microscopic brain damage, as well as reduced amyloid accumulation [63] and oxidative stress; the combination of both vitamins C and E has proved superior than supplementation with either alone [79]. This is evident by the reduced brain injury due to oxidative stress following their supplementation.

Patients supplemented with vitamin E after severe TBI experienced decreased mortality and increased Glasgow outcome scores, and had decreased edema and lesion size when treated with vitamin C. Treatment with both, however, was better than each treatment alone. Both vitamins are readily available, but vitamin E can cause hemorrhage at high dosages. Further studies are needed to evaluate their efficacy in sports concussions and recommend an appropriate supplementation dose for therapy.

Nicotinamide Ribose

Nicotinamide, or vitamin B3, is a precursor of neuronal nicotinamide adenine dinucleotide (NAD+). Its involvement in the many cellular metabolic and immune responses to pathophysiologic stress mechanisms makes it a subject of interest. Additionally, studies reported its enhanced ability to attenuate mediators of axonal degeneration when supplemented in rodents recovering from brain injury [80]. Elevated NAD concentrations reduced the damage caused by Sterile alpha and TIR motif-containing 1 (SARM1) protein, an essential mediator of axonal death during injury and disease [81]. An ongoing human clinical trial is currently being conducted to observe its effect in American football athletes (NCT02721537). No dosage recommendations have been proposed, but sources of nicotinamide ribose include dairy milk, yeast, and beer [80].

Melatonin

Melatonin is a hormone secreted by the pineal gland in the brain and is primarily responsible for regulating the sleep-wake cycle. It is commonly used to alleviate jet lag symptoms and adjust nocturnal rhythms in travelers. Its antioxidative, anti-apoptotic, neuroprotective, and anti-inflammatory properties [82] make it worth exploring as an alternative treatment in concussive head injuries, especially since sleep-wake disturbances are common following TBI [83]. Sleep disturbances have been shown to prolong healing and recovery times after concussions and affect the severity of post-concussive symptoms in athletes and nonathletes alike [84].

Brain injury seems to disrupt the synthesis and production of melatonin. Patients who experienced mild-severe TBIs have shown decreased sleep efficiency, increased

wake after sleep onset, delayed melatonin secretion, and significantly lower levels of evening melatonin production associated with less rapid eye movement (REM) sleep when compared to controls [83]. Melatonin has showed neuroprotective properties in animals following TBI [82]. Additionally, a systematic review in children with TBIs concluded that melatonin appears to be promising for the management of sleep impairment [85] and another similar clinical trial by the University of Calgary is currently underway (NCT01874847). Melatonin may also be effective in treating and decreasing the frequency of primary headache disorders such as migraines and cluster headaches which represent another common complaint throughout the delayed phase of concussive symptoms [86].

Melatonin is a widely available safe supplement that holds promise in the management of sports concussions sleep symptoms. A dose of 0.5–5 mg, followed by a maintenance dose after realignment, has been suggested. Further studies are warranted to validate its use and effectiveness in sports concussions.

Caffeine

Caffeine, the most commonly used psychoactive agent in the world, is a central nervous system stimulant of the methylxanthine class. It also affects the cardiovascular system and is extremely popular worldwide, especially among athletes. It is known to enhance memory, alertness, and physical performance. It is of concern to the concussive sports patient because of its alternating effects in the short- versus long-term. Caffeine inhibits the adenosine 1 (A1) and A2A receptors [87] responsible for suppressing glutamate release and excessive inflammatory cytokine production [88]. It therefore interferes with the neuroprotective actions of adenosine in ischemic-hypoxic conditions. The adverse outcomes as a result of caffeine supplementation in mild TBI [88] are possibly due to the increased intracellular calcium concentration and activation of adenylyl cyclase, as a result of IP-3 receptor stimulation [87].

Conversely, the chronic ingestion of caffeine has shown to be beneficial in animal and humans experiencing severe TBI [88, 89]. The difference in effectiveness of caffeine between mild and severe TBIs could be explained by the differences in cAMP concentrations in CSF. The elevated CSF caffeine levels following severe TBI in humans showed outcome benefits [89]. This could be due to the increased A1 receptor expression following chronic caffeine ingestion, which helps suppress inflammation and glutamate release.

Caffeine is widely available as a supplement, and is found in tea, chocolate, soft drinks, and energy drinks. No dosage recommendations have been suggested, but further studies are needed to determine its efficacy, safety, and adverse effect profiles following TBI. Physicians involved in neurocognitive testing and return of play following concussion should take note of altered reaction times following caffeine ingestion close to assessment.

Green Tea

Green tea is produced from the leaves of the plant species *Camellia sinensis* (L.) Kuntze [89]. It is among the most popular consumed beverages and has shown to possess pharmacologically active polyphenols that are of benefit to a variety of diseases, including cancer, obesity, diabetes, cardiovascular disease, and neurodegenerative diseases. Its antioxidant and anti-inflammatory properties make it a subject of interest in the management of concussive head injuries.

Tea polyphenols directly scavenge reactive oxygen and nitrogen species, inhibit the activity of nitric oxide synthase, xanthine oxidase, cyclooxygenases, lipoxygenases, NF-κB, and activator protein-1. Epigallocatechin-3 galate (EGCG) is the most abundant polyphenol or catechin in green tea and is behind many of those anti-inflammatory and neuroprotective benefits. Studies have shown that EGCG inhibits TNF-α activation of IL-8 gene expression through the inhibition of NF-κB [89]. The inhibition of NF-κB is achieved by inhibiting the degradation of IL-1 receptor-associated kinase (IRAK), an enzyme responsible for the activation of NF-κB, or by interfering with the cell receptor binding of IL-1β [90]. EGCG may also have post-transcriptional anti-inflammatory effects by destabilizing proinflammatory mRNA [90]. The neuroprotective benefits of EGCG have been mainly observed in neurodegenerative diseases. This is through the inhibition of *N*-methyl-D-aspartate-induced cellular damage in neurons and the production of antioxidant enzymes such as glutathione S-transferases and superoxide dismutase. EGCG was also found to suppress the neurotoxicity induced by Aβ, as it activates glycogen synthase kinase-3β (GSK-3β) and inhibits the cytoplasmic nonreceptor tyrosine kinase Abl/FE65, which is primarily involved in neuronal development and nuclear translocation [91].

Green tea and its extracts are safe and widely available for use. The usual recommendation is around 300–400 mg/day or around four cups, but further studies are needed to validate its efficacy in mild TBIs.

Branched Chain Amino Acids

Branched-chain amino acids (BCAAs) have an aliphatic side chain and a branch. They are abundant in humans and comprise almost one-third of all amino acids present in our bodies. The three known proteinogenic BCAAs, valine, leucine, and isoleucine, play a vital role in muscle protein synthesis and have been popularized among athletes and bodybuilders as muscle building supplements. They also cross the BBB and contribute to the synthesis of neurotransmitters glutamate and gamma aminobutyric acid. Neurometabolic cascades associated with concussive brain injuries have been shown to decrease levels of BCAAs [92] and their supplementation following severe TBI allowed patients to exhibit cognitive benefits per disability rating scale scores [91]. BCAAs are the building blocks of protein and are found in meats, dairy, nuts, beans, and are also available in pill or powder form. Further research is required to examine their effect in mild TBI and supplementation in sports concussions.

Creatine

Creatine is an amino acid naturally synthesized in gastrointestinal tract from the amino acids glycine, arginine, and methionine [90]. It is phosphorylated by creatine kinase to phosphocreatine [90] to supply metabolically active areas of the body, such as skeletal muscles, heart, and brain with energy. It is among the most studied supplements in sports science and is popular among athletes that seek to increase their strength performance and muscle building activities [90]. Studies have shown neuroprotective effects in animals subjected to a creatine rich diet following brain injury [93]. This is of particular importance because creatine and phosphocreatine levels are decreased after mild TBI.

Neuroprotection is believed to be related to the maintenance of mitochondrial bioenergetics. This is achieved by the replenishment of cellular ATP levels, resulting in the reduction of mitochondrial permeability, free oxygen radicals, and calcium levels. In pediatric patients, creatine supplementation following severe TBI improved short- and long-term outcomes. This included less time being intubated, less time in the intensive care unit, and improved amnesia acutely; and communication, behavior, and cognitive benefits long-term [94]. Creatine is widely available as a supplement and can also be obtained from protein rich foods such as poultry, meat, and fish. It is often dosed at 5 g/day, but further studies are needed to validate its use in mild TBIs and sports concussions.

Key Learning Points

- The majority of sports-related concussive episodes (80–90%) resolve spontaneously in 7–10 days.
- Nonpharmaceutical therapies include O3FAs, resveratrol, vitamin D, curcumin, magnesium, vitamins B3, E, C, melatonin, green tea, creatine, BCAAs, and caffeine, among others.
- FDA has not approved the use of any dietary supplement or alternative therapies for the prevention of concussions or the reduction of post-concussion symptoms.

Conclusions

We have described the use and scientific basis of several anti-inflammatory supplements or alternative remedies that have shown to attenuate brain injury, excitotoxic cell signaling, and microglial activation. More recently, additional alternative therapies have been explored in the management of concussive head injuries and headaches with varying effects, including cranial nerve blocks, botulinum toxin injections**,** acupuncture, transcranial direct stimulation, physiotherapy, electroconvulsive therapy, and hyperbaric oxygen [5, 95, 96].

In general, little has been investigated regarding the management of sports concussions with supplements and medications. As of now, the FDA has not approved

the use of any dietary supplement for the prevention of concussions or the reduction of post-concussion symptoms. Long-term clinical trials are still required to document their efficacy in humans, particularly in regard to mild TBIs. Compared to other forms of concussions (assault or collision), sports-related concussions seem less likely to result in PCS [1]. Though, PCS can be devastating to athletes and their careers, and require further medical attention along with the appropriate social support. Prevention is certainly the most important step in management, followed by the initial recognition of a concussive episode and prompt management.

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