

The Role of Nutritional Supplements in Sports Concussion Treatment

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Abstract

There has been considerable research conducted in regard to the prevention and treatment of concussions. Numerous supplements and vitamins are being used throughout the country to help patients recover from concussions; however, to date, there are no completed human-based studies specifically examining supplement and vitamin use for the treatment or prevention of concussions. This article examines the most current evidence regarding supplements and vitamins for the treatment and prevention of concussions. The supplements and vitamins reviewed include omega-3 fatty acids, curcumin, resveratrol, melatonin, creatine, and *Scutellaria baicalensis*.

work in overdrive to reestablish equilibrium, thereby depleting the brain energy stores. Initially hyperglycolysis occurs to generate more ATP because it has been depleted, but this leads to the accumulation of lactate and causes an influx of Ca^{2+} , which is sequestered into the mitochondria and impairs oxidative metabolism (increased reactive oxygen species production) ATP production, and glucose metabolism. The influx of Ca^{2+} also activates the protein calpain and leads to apoptosis and cell death. The brain initially becomes

Introduction

Can supplements play a role in concussion management? Not at this time. Currently there is no strong evidence to support the use of supplements for concussion management; however there are numerous animal-based studies with promising results as well as human trials with severe traumatic brain injury (sTBI) showing great potential. There are four human trials evaluating the use of supplements in concussion management, but they have not been completed.

To get a better understanding of how certain supplements may aid in the treatment of concussions, it is important to understand the neuromolecular cascade that occurs in the brain after a concussion, which has been best studied in sTBI models. A patient sustains a concussion which causes a disruption of neuronal cell membranes and stretching of axons. This disruption and stretching causes an indiscriminate flux of ions (potassium and calcium) through previously regulated ion channels as well as through transient physical membrane defects. The ionic influx then causes a widespread release of excitatory neurotransmitters (especially glutamate), which in turn leads to more efflux of potassium. Now the Na/K/ATPase-dependent pump has to

hypermetabolic to supply enough ATP, but this occurs during decreased cerebral blood flow, and this disparity sets up an energy crisis that could leave the brain vulnerable to responding to a second injury, especially with sports-related concussions (3,18,25). Occurring at the same time in the neuronal axons, as a result of being stretched, a calcium influx causes neurofilament compaction and microtubule disassembly, which leads to an accumulation of axonally transported organelles causing axonal swelling with eventual axotomy (3,18).

Numerous supplements, including omega-3 fatty acids (O3FA), curcumin, resveratrol, melatonin, creatine, and *S. baicalensis* as well as vitamins C, D, and E, have shown promising results in animal studies, most using a fluid percussion technique to cause the injury, as well as a few human studies concerning sTBI, to aid in the recovery or the prevention of concussion by acting on one or more aspects of the neuromolecular cascade.

O3FA

There have been numerous animal-based studies (mainly in rats) investigating the effects of O3FA, particularly docosahexaenoic acid (DHA), on the treatment and prevention of concussions. Research has shown that supplementation with O3FA before sustaining a concussion can protect against reduced plasticity of neurons and impaired learning by normalizing levels of proteins associated with neuronal circuit function, cognitive processing, synaptic facilitation, neuronal excitability, and locomotor control (41). It also has been

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shown that supplementation with O3FA before a concussion can reduce biological markers of brain injury and cellular apoptosis (28). O3FA also can protect against reduced plasticity and impaired learning as well as provide resistance to oxidative stress created from a concussion (43). Supplementation with O3FA after sustaining a concussion also can help maintain genomic stability and cellular homeostasis (42) as well as decrease the amount of injury the brain sustains (2).

These previous findings show great potential; however, as of now, there have not been any human studies with a high level of evidence to confirm these. There is one case report that has helped further advance the research of O3FA in head injuries. A teenage boy experienced sTBI from a motor vehicle accident, which led to a persistent vegetative state. After starting O3FA supplementation, he exhibited a significant clinical improvement and was able to walk for his high school graduation 3 months later (23).

Currently, there are two double-blind randomized control trials examining DHA supplementations and concussions. David Bica, DO, and Joseph Armen, DO, at East Carolina University are supplementing the NCAA division 1 athletes with 2200 mg of DHA for 30 days after onset of a concussion and measuring the number of days for full unrestricted participation and the number of days for balance and cognition to return to baseline (9). Shane Miller, MD, at the University of Texas Southwestern Medical Center is supplementing kids ages 14 to 18 years with 2 g of DHA daily for 3 months and measuring the time to return to competitive play and resolution of balance impairment (27). Both of these studies are in progress and do not have any preliminary data to share.

Curcumin

Curcumin, one of the phytochemicals in turmeric, is another supplement that shows promise for the treatment of concussion. Animal-based studies have shown that supplementation with curcumin before sustaining a concussion resulted in improved balance as well as transduction and monitoring of cellular energy compared with controls (34). Supplementation with curcumin after a concussion has been shown to improve membrane function, restoration of homeostasis, neuronal plasticity (35), synaptic plasticity, and neuronal signaling (44) as well as significantly reduced neural inflammation by decreasing the levels of microglia and macrophages that aid in neuronal apoptosis (50). However, there have been no human trials to date and currently there are not any human trials in the process of evaluating the effects of curcumin and concussion.

Resveratrol

Resveratrol, a polyphenol found in abundance in red wine, plants, and nuts, has been shown to have antioxidant effects (13). There have not been many studies evaluating the effects of resveratrol on treating concussions. Resveratrol has been shown to be a powerful antioxidant (13) and that it exerts neuroprotective effects in degenerative neurological diseases (31). The two animal studies evaluating resveratrol in regard to treatment of concussions did find that supplementation with resveratrol after a concussion can increase cell survival by suppressing autophagy and apoptosis that are mediated by a pathway induced by glutamate

toxicity (24) as well as improve motor performance, visual spatial memory, and behavior (36). There is one human trial currently ongoing at the University of Texas Southwestern Medical Center headed by Joshua Gatson, PhD, in which they are evaluating the use of resveratrol in boxers who have sustained a mild to moderate concussion (REPAIR study). The study is a double-blind, placebo-controlled randomized control trial measuring cognitive performance with ImPACT testing and axonal injury via magnetic resonance imaging. This study has been completed, but there has not been any data published (17).

Melatonin

Melatonin, a hormone produced mainly by the pineal gland known to regulate circadian rhythms (46), is another supplement with neuroprotective properties. Animal-based studies have shown that melatonin can decrease brain edema and intracranial pressure as well as the permeability of the blood brain barrier (6,14,21). Melatonin has been shown to restore levels of oxidative stress markers (47), mitigate the damage of reactive oxygen species (8), and decrease the release of pro-inflammatory cytokines (15). Melatonin also has shown some value in animal models as a neuroprotective drug against Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (29). However, these neuroprotective effects have not been studied in actual human models, and the only double-blind, placebo-controlled randomized trial taking place is examining the use of melatonin in children who have encountered a concussion and are having subsequent sleep issues. This clinical trial is ongoing with a planned end date in 2019 (Play Game Trial) (4).

Creatine

Creatine, a supplement most well known for aiding in muscle mass growth with weight lifting, also has shown promise for the treatment of concussions. Biochemically, creatine works in the CNS by donating a phosphoryl group to ADP to make ATP and help replenish energy stores (7), thereby theoretically decreasing hyperglycolysis and oxidative damage. Using proton magnetic resonance spectroscopy to measure the levels of creatine pre- and postconcussion, it is now known that creatine levels in the brain decrease after sustaining a concussion (39). There have been two human-based randomized prospective studies using creatine supplementation in children after sustaining a moderate to severe TBI. These studies, which were open label, showed that compared with the control group, the children who were supplemented with creatine had significantly improved cognition, communication, self-care, personality, and behavior (32) and significantly decreased headaches, dizziness, and fatigue (33). Based on these studies, creatine shows promise for the treatment of concussions; however, given that these studies were evaluating patients with sTBI with a longer time to recovery, it is not known if creatine would improve outcomes in patients with concussions whose symptoms are generally resolved in under 2 wk.

Vitamins

Vitamins C, D, and E have been studied more than other vitamins in the treatment of concussions. Vitamin E, or alpha-tocopherol, has been studied in numerous rodent

models, and it was shown that supplementation with this vitamin increases brain levels (12). Rats treated with vitamin E after a concussion had decreased functional neurological deficits and microscopic brain damage (45) as well as a decreased amount of lipid peroxidation (oxidative stress) and amyloid accumulation (12). When vitamin C is supplemented with vitamin E, there is a significantly less amount of brain injury due to oxidative stress than supplementation with either vitamin E or vitamin C alone (20). Vitamins C and E supplementation has been studied in humans who have sustained sTBI. In patients who presented with a Glasgow Coma Scale score less than or equal to 8 and had radiographic evidence of diffuse axonal injury, had decreased mortality, and increased Glasgow Outcome Scores if treated with vitamin E and decreased edema and lesion size if treated with vitamin C (30). Recently, cells in the CNS have been shown to have vitamin D receptors that modulate gene transcription responsible for neuronal proliferation and maintenance of calcium homeostasis (16). By itself, vitamin D has not shown great promise for traumatic brain injuries, though in combination with progesterone, there are some promising results. In a rodent study, the combination of progesterone and vitamin D showed significantly reduced neuronal loss and proliferation of reactive astrocytes after a traumatic brain injury (37). In the two human-based studies, the combination of progesterone and vitamin D in patients with sTBI resulted in significantly improved Glasgow Outcome Scale scores, a better recovery rate (1), and a greater efficacy in reducing neuroinflammation (38). Like creatine, vitamins C, D, and E have shown utility in the use of severe brain trauma; however, at this time, more research is needed for their use in concussions.

S. baicalensis

S. baicalensis, an herb containing three flavonoids (baicalein, baicalin, and wogonin), is a widely used Chinese herbal medicine. *In vitro* studies have shown that *S. baicalensis* decreased neuronal oxidative stress and decreased apoptosis (26,49). Animal models designed to mimic Alzheimer's and chronic hypoperfusion demonstrated that the *S. baicalensis* decreased neuronal cell damage and decreased motor and cognitive impairments by decreasing reactive oxygen species production (19,48). Animal models using *S. baicalensis* after a traumatic brain injury have been examined also, and it was found that treatment with *S. baicalensis* decreased brain edema, inflammatory mediators, microglial activation, and cell death as well as increased overall neurological function (10,11,40). To date, no human trials have been completed examining *S. baicalensis* for the treatment or prevention of concussion.

Discussion

There are some promising animal-based studies showing that certain supplements may be beneficial for the prevention and treatment of concussions. There also are human studies showing promise with certain supplements and sTBI. However, currently there is no good human evidence that these supplements can help in the treatment or prevention of concussions. Hopefully the human trials that are currently ongoing can provide us with more information, but we also must take into account the easy accessibility of

supplements and a possible false sense of security athletes may get if they are taking these supplements. What is not wanted is a football player thinking he can now hit helmet to helmet because he has been taking one of the above supplements. If it is found that some of these supplements can aid in the treatment or prevention of concussions, athletes need continual education to decrease or eliminate any false sense of security. It is important to understand that supplements are not subject to the safety and quality standards of the Food and Drug Administration. Because of this, the potency of an individual supplement is unknown. A study done in 2013 showed that only 1/3 of vitamin D supplements tested met the U.S. Pharmacopeial Convention standards requiring pills to contain between 90% and 100% of the active ingredient. The study also found a large amount of variability in the active ingredient ranging from 9% to 146% (22). It remains vitally important to continue to teach athletes about concussions, to make sure all athletes are reporting concussions, and to not have athletes return to play until they are back to their baseline and have progressed through the return to play protocol. Supplements may play a role in the management of concussions in the near future, but currently the evidence does not support their use.

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