

The Role of Dietary Supplements in Treatment of Traumatic Brain Concussion in Athletes

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Abstract

Brain concussion is a common type of trauma, particularly in sports. Many dietary supplements and/or vitamins are used to help the injured patients to improve their clinical condition after brain concussions. However, up to date, there are no comprehensive human-based studies that specifically document the use of supplements and vitamins for the treatment or prevention of brain concussion. An extensive bibliographic review in Greek and international databases was conducted in order to collect studies and articles about the prevention and treatment of brain concussion in athletes. This article reviews the latest data about the use of supplements and vitamins in treatment and prevention of concussion in athletes as a result of injuries. The vitamins and supplements presented-discussed in this article, include omega-3 fatty acids, curcumin, resveratrol, melatonin, creatine and Scutellaria baicalensis.

Key words: concussion, athletes, concussion therapy, nutritional supplements

1 Introduction

At this time supplements cannot play a role in concussion management as there is not great evidence supporting their use for concussion management. Nevertheless, there are many animal-based studies with promising results as well as human trials with severe traumatic brain injury (sTBI) that show great potential. [1] There are four incomplete human trials which evaluate the use of diet supplements in concussion management. [1]

For a better understanding of how specific supplements may contribute in the treatment of concussions, it is crucial to understand the neuromolecular cascade that occurs in brain after a concussion, which has been studied in sTBI models. The concussion causes a disruption of neuronal cell membranes and stretching of axons. These two situations cause an indiscriminate flux of ions (potassium and calcium) through previously regulated ion channels as well as through transient physical membrane defects. As a consequence, the ionic influx causes a release of excitatory neurotransmitters (especially glutamate), which in turn leads to more efflux of potassium. The Na/K/ATPase-dependent pump has to work in overdrive to reestablish equilibrium, thereby depleting the brain energy stores. Initially, hyperglycolysis occurs in order to produce more ATP due to the fact that it has been depleted, but this leads to the accumulation of lactate and causes an influx of Ca²⁺, which is sequestered into the mitochondria and impairs oxidative metabolism (increased reactive oxygen species production) ATP production, and glucose metabolism. The influx of Ca²⁺ also activates the protein calpain and leads to apoptosis and cell death. The brain initially becomes hypermetabolic to supply enough ATP, but this happens 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 [2-4].

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Simultaneously, in the neuronal axons, as a consequence of being stretched, a calcium influx causes neurofilament compaction and microtubule disassembly that leads to an accumulation of axonally transported organelles causing axonal swelling with eventual axotomy [2,3].

Numerous supplements, including omega-3 fatty acids (O3FA), resveratrol, curcumin, creatine, melatonin and *S. baicalensis* as well as vitamins C, D, and E, have shown promising results in both animal and human studies concerning sTBI, aiding in the recovery or even the prevention of concussion by acting on one or more aspects of the neuromolecular cascade.

2. Categories of Diet Supplement for Concussion Management

2.1. Omega-3 Fatty Acids-O3FA

There have been many animal-based studies (mainly in rats) that investigate the effects of O3FA, in particular docosahexaenoic acid (DHA), about the treatment and prevention of concussions [1]. Studies have shown that supplementation with O3FA before sustaining a concussion may protect against decreased plasticity of neurons and impaired learning by regularizing levels of proteins associated with neuronal circuit function, cognitive processing, neuronal excitability, synaptic facilitation and locomotor control [5]. Moreover, it has been shown that supplementation with O3FA before a concussion may reduce biological markers of brain injury and cellular apoptosis [6]. O3FA also may protect against decreased plasticity and impaired learning as well as grant resistance to oxidative stress that is created from a concussion [7]. Supplementation with O3FA after sustaining a concussion may aid in maintaining genomic stability and cellular homeostasis [8] and in decreasing the amount of injury the brain tolerate [9].

Although these findings show great potential, there are not any confirmative human studies with strong evidence. In bibliography, there is one case report that has further contributed at the research of O3FA in head injuries. [10] It is about a teenager who experienced sTBI from a motor vehicle accident, which led to a persistent vegetative state. After beginning O3FA supplementation, he exhibited a significant clinical improvement and was able to walk for his graduation after 3 months [10].

At this time, there are two double-blind randomized control trials examining DHA supplementations and concussions [11]. Researchers from East Carolina University supplemented athletes from NCAA division 1 with 2200 mg of DHA for 30 days after onset of a concussion and measured the number of days to full unrestricted participation and the number of days for balance and cognition to return to baseline [11]. Moreover, researchers from University of Texas Southwestern Medical Center supplemented kids ages 14 to 18 years with 2 gr of DHA daily for 3 months and measured the time to return to competitive play and resolution of balance impairment [12]. Both of these studies are in progress and there are not any preliminary data to be shared [1].

2.2. Curcumin

Curcumin is another promising diet supplement for the treatment of concussion. Animal-based studies have shown that supplementation with curcumin before sustaining a concussion resulted in better balance as well as transduction and monitoring of cellular energy compared with controls [13]. Supplementation with curcumin after a concussion has been shown to ameliorate membrane function, restoration of homeostasis, [14] neuronal plasticity, neuronal signaling and synaptic plasticity [15] as well as significantly decreased neural inflammation by reducing the levels of microglia and macrophages that contribute in neuronal apoptosis [16]. Nevertheless, there have not been human trials about the evaluation of the effects between curcumin and concussion.

2.3. Resveratrol

Resveratrol, a polyphenol that is found in abundance in red wine, plants, and nuts, has been shown to have antioxidant effects [17]. There have not been many studies evaluating the effects of resveratrol on treating concussions. Resveratrol has been considered to be a powerful antioxidant and that it exerts neuroprotective effects in degenerative neurological diseases [17, 18]. There are two animal studies evaluating resveratrol in regard to treatment of concussions that found supplementation with resveratrol after a concussion may increase cell survival by suppressing autophagy and apoptosis mediated by a pathway induced by glutamate toxicity [19] as well as enhance motor performance, behavior and visual spatial memory [20]. There is one human trial

currently ongoing at the University of Texas Southwestern Medical Center in which researchers 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 are not any data published [21].

2.4. Melatonin

Melatonin is another supplement with neuroprotective properties [22]. Animal-based studies have shown that melatonin may reduce brain edema, intracranial pressure and the permeability of the blood brain barrier [23-25]. It has been shown that melatonin may restore levels of oxidative stress markers [26], mitigate the damage of reactive oxygen species [27] and reduce the release of pro-inflammatory cytokines [28]. Furthermore, melatonin has been shown to be a neuroprotective drug against Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis, according to some animal models [29]. However, these neuroprotective effects have not been studied in actual human models. The unique double-blind, placebo-controlled randomized trial that is being held, is examining the use of melatonin in children who have sustained a concussion and are experiencing subsequent sleep issues. This clinical trial is ongoing with a planned end date in 2019 (Play Game Trial) [30].

2.5. Creatine

Creatine, a supplement most known for its role in muscle mass growth and power lifting, also has been considered to be promising for the treatment of concussions. Creatine works in the CNS by donating a phosphoryl group to ADP to make ATP and help restoring energy stores [31], and thus, theoretically, decreasing hyperglycolysis and oxidative damage. Using proton magnetic resonance spectroscopy to measure the levels of creatine before and after the concussion, it is currently known that creatine levels in the brain decrease after a concussion [32]. There have been two human-based randomized prospective studies using creatine supplementation in children after sustaining moderate to severe TBI.

These studies, which were open label, revealed that compared with the control group, the children who were supplemented with creatine had significantly improved cognition, communication, self-care, behavior and personality, as well as significantly decreased dizziness, headaches and fatigue [33, 34]. Based on these studies, creatine shows potential for the treatment of concussions. However, given that these studies evaluated 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 weeks.

2.6. Vitamins

Vitamins that have been studied the most in the treatment of concussions are vitamins C, D and E. Vitamin E has been studied in many rodent models, and it has been shown that supplementation with this vitamin boosts brain levels [35]. Rats that are treated with vitamin E after a concussion, had decreased functional neurological deficits, microscopic brain damage and a reduced amount of lipid peroxidation (oxidative stress) and amyloid accumulation [35, 36]. 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 [37].

Vitamins C and E supplementation have been studied in humans that sustained sTBI. In patients presented with a Glasgow Coma Scale score less than or equal to 8 and had radiographic evidence of diffuse axonal injury, had decreased mortality rates and increased Glasgow Outcome Scores if treated with vitamin E and reduced edema and lesion size if treated with vitamin C [38]. 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 [39]. Although vitamin D has not shown promising results for traumatic brain injuries by itself, in combination with progesterone, there are some promising results. In a rodent study, the combination of progesterone and vitamin D showed significantly decreased neuronal loss and proliferation of reactive astrocytes after a TBI [40]. In 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, and a greater efficacy in reducing neuroinflammation [41, 42]. Like creatine, vitamins C, D, and E have shown utility in the use of severe brain trauma. However, at this point, more research is needed for their use in concussion treatment.

2.7. *S. baicalensis*

S. baicalensis, an herb that contains three types of flavonoids (baicalein, baicalin, and wogonin), is a widely used Chinese herbal medicine. In vitro studies, it is shown that *S. baicalensis* reduced neuronal oxidative stress and decreased apoptosis [43,44]. Animal models designed to mimic Alzheimer's disease and chronic hypoperfusion demonstrated that the *S. baicalensis* reduced neuronal cell damage and decreased motor and cognitive impairments by decreasing reactive oxygen species production [45,46]. Animal models using *S. baicalensis* after a TBI have been also examined, and it was found that treatment with *S. baicalensis* decreased brain edema, inflammatory mediators, microglial activation, cell death and increased the overall neurological function [47-49]. Up to date, there are no human trials completed, which examined *S. baicalensis* for the treatment or prevention of concussion.

3. Discussion

There are some promising animal-based studies showing that certain diet supplements can be beneficial for the prevention and treatment of concussions. There also are human studies showing potential with certain supplements and sTBI. However, currently there is no strong human evidence that these diet supplements may contribute in the treatment or prevention of concussions. Hopefully the human trials currently ongoing, may provide more information, but the easy accessibility of supplements and a possible false sense of security athletes may get if they are taking these supplements, must be taken into account. What is not wanted, is a football player that thinks 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 diet supplements can help at the treatment or prevention of concussions, athletes need continuous education to reduce or eliminate any false sense of security. It is important to underline and unsterstad that supplements are not subject to the safety and

quality standards of the Food and Drug Administration. Due to this fact, the potency of an individual supplement is unknown. A research paper 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 [50]. The study also found a large amount of variability in the active ingredient ranging from 9% to 146% [50]. It remains crucial to continue to educate and inform 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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