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General review

# Nutritional factors in sport-related concussion

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ABSTRACT

*Background.* – Sports concussion is a major problem that affects thousands of people every year. Concussion-related neurometabolic changes are thought to underlie neurophysiological alterations and post-concussion symptoms, such as headaches and sensitivity to light and noise, disabilities of concentration and tiredness. The injury triggers a complex neurometabolic cascade involving multiple mechanisms. There are pharmaceutical treatments that target one mechanism, but specific nutrients have been found to impact several pathways, thus offering a broader approach. This has prompted intensive research into the use of nutrient supplements as a concussion prevention and treatment strategy.
*Method.* – We realised a bibliographic state of art providing a contemporary clinical and preclinical studies dealing with nutritional factors in sport-related concussion.
*Results.* – Numerous supplements, including n-3 polyunsaturated fatty acids, sulfur amino acids, antioxidants and minerals, have shown promising results as aids to concussion recovery or prevention in animal studies, most of which use a fluid percussion technique to cause brain injury, and in a few human studies of severe or moderate traumatic brain injury. Current ongoing human trials can hopefully provide us with more information, in particular, on new options, i.e. probiotics, lactate or amino acids, for the use of nutritional supplements for concussed athletes.
*Conclusion.* – Nutritional supplementation has emerged as a potential strategy to prevent and/or reduce the deleterious effects of sports-related concussion and subconcussive impacts.


## 1. Introduction

Mild traumatic brain injury (TBI), or 'concussion', is caused "by a direct blow to head, face, neck or elsewhere on the body with an 'impulsive' force transmitted to the head" [1]. In the United States, sport is the second-leading cause of TBI in 15–24-year-olds, only behind motor vehicle crashes [2]. Concussion is associated with cognitive impairment and other symptoms, such as headaches and sensitivity to light and noise, disabilities of concentration and tiredness [3], which in turn may lead to mood swings and academic issues, particularly in older adolescents and young adults. This makes concussion an important public health concern.

The number of sport-associated concussions has been increasing steadily in recent years, regardless of the sport considered, with contact sports predominating. In the contact sports population, the syndrome of reduced brain resilience leads to increased susceptibility to concussions. This syndrome is a particular physiological state corresponding to functional nutrient deficits and disturbances of certain mechanisms that normally maintain metabolic homeostasis in brain tissue. The brain is a very special tissue with exceptional metabolic constants compared to other tissues. For example, it uses 20% of all ingested calories and requires more than 40 different nutrients to function properly. The brain thus has important specific nutritional needs. It is a high-metabolic-rate tissue with a huge need for energy substrates, mainly in the form of glucose, as well as specific needs for certain essential nutrients, including some n-3 polyunsaturated fatty acids (PUFA) and amino acids (AA).

## 2. Methodology

Studies, which contained data on nutritional factors in sport-related concussion, were identified using the electronic database Pubmed. Search terms included words and synonyms for:

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(nutritional needs or nutritional supplementation or nutrient or nutrition or food or diet) AND (concussion or mild traumatic brain injury or sport-related concussion) AND (athlete or sport or exercise or physical activity or contact sport). Reference lists of all selected reports were also reviewed to identify additional eligible manuscripts.

## 3. Metabolic changes in the brain after concussion

Practicing sport or physical activity increases brain function and thus increases nutrient use by brain tissue. Furthermore, research has found areas of elevated brain activation corresponding to increased nutrient utilisation in athletes participating in contact sports compared to non-contact sports [4], and it was recently shown that concussions cause overconsumption of nutrients by the brain [4,5].

The biochemical processes related to concussion begin with axonal stretching, leading to possible mitochondrial dysfunction [6,7]. Specifically, axonal stretching causes a massive efflux of $K^+$ ions [8] and a release of abnormally large amounts of excitatory neurotransmitters, especially glutamate [8,9], resulting in a large influx of $Ca^{2+}$ ions, thus further depolarising the cell [10,11]. To restore the ion gradient, the cell activates $Na^+/K^+$ pumps requiring additional adenosine triphosphate (ATP) to try to recover the lost $K^+$ [12,13]. To sustain this cellular demand, the cell resorts to glycolysis, using 40% more glucose than normal [14], and leading to lactate accumulation [15] and a concomitant fall in intracellular pH [14,16].

Thus, concussions cause ionic and metabolic modifications that induce an increase in the use of glucose and other nutrients like AA. It has been postulated that altered AA metabolism after TBI likely contributes to decreased energy production and neurotransmitter synthesis and may contribute to the pathophysiology of TBI [17]. Concussion also leads to increased inflammation and oxidative stress, which accelerate the use of anti-inflammatory and antioxidant nutrients [18]. Tissue reconstruction is also accelerated after brain injury, generating an increased needs for certain nutrients involved in the mechanisms that regulate brain plasticity (n-3 PUFA, vitamins B and D, AA) [19].

Overall, then, the brain changes in response to concussion are largely related to changes in energy consumption, i.e. increased ATP utilisation, leading to hyperglycolysis followed by hypoglycolysis, resulting in abnormal pH [20]. Taken together, the evidence shows that the nutritional needs of the brain are modified during sport practice, especially in contact and collision sports, thus increasing the risk for concussion.

## 4. Nutritional needs of the brain after concussion

From the food and nutrition standpoint, the objectives in a context of concussion are therefore to reduce the energy crisis, promote the repair of cell membranes, reduce ionic losses, and regulate protective mechanisms. In practice, for any athlete, the first thing to do is to chronically adopt a balanced, varied, complex diet composed of well-chosen, good-quality, relatively unprocessed foods.

However, today's food trends have significantly reduced the bioavailability of neuro-critical nutrients, i.e. able to protect the brain-tissue structures and preserve homeostatic brain-tissue metabolism. Decreasing the body status in these neuroprotective nutrients triggers physiological and biochemical 'bypass' processes that can make brain-tissue more sensitive and less adaptive to shocks to the head. For example, reducing antioxidant capacities alters the critical post-concussion protective buffer and repair mechanisms. A depletion of certain minerals together with overconsumption of heavily-processed foods that are deficient in key nutrients for brain tissue, such as n-3 PUFA, compromises the resistance and resiliency of the brain. In fact, significant changes in lifestyle practices, such as the use of a largely more complex and less processed diet, could significantly reduce neurological damage due to sport-related concussion.

Recent scientific research also reports promising positive effects of dietary supplements composed of nutrients with neuroprotective properties. Increased consumption of n-3 PUFA, especially docosahexaenoic acid (DHA), or certain amino acids such as cysteine, and food fortification with micronutrients, particularly the minerals involved in brain resiliency, such as sulfur, zinc and magnesium, have emerged as potential nutritional strategies to help prevent concussion and its consequences in athletes. Treatment with magnesium was found to significantly improve long-term neurological outcome in rats after fluid-percussion TBI [21]. There are a variety of reasons why magnesium may improve neurological outcome following experimental brain injury. The magnesium ion is essential for a number of important cellular and enzymatic processes, including glycolysis, oxidative phosphorylation, protein synthesis, DNA and RNA aggregation, and maintenance of plasma membrane integrity. Since intracellular magnesium concentrations fall markedly after TBI, post-injury treatment with magnesium may serve to restore the functional ability of the cell to perform these processes. Interestingly, it was also found that pretreatment with magnesium can prevent the post-trauma decline of intracellular free magnesium [16,22].

The cascade of metabolic, cellular and molecular events related to extensive tissue destruction and repair partly involves disruption in mitochondrial capacity to scavenge reactive oxygen species (ROS) [23]. N-acetyl-cysteine (NAC), a thiol-containing AA, replenishes glutathione synthesis [24], and may thereby ameliorate secondary brain injury as it counters the deleterious effects of oxidative stress, promotes redox-regulated cell signalling, and dampens excessive immuno-inflammatory responses [25]. Evidence from the animal literature demonstrates that prophylactic application of NAC post-TBI is robustly associated with improved neuro-functional outcomes and downregulation of inflammatory and oxidative stress markers at tissue level [23]. A human study, conducted in an active theatre of war, also demonstrated that NAC has beneficial effects on severity and resolution of sequelae following blast-induced TBI [26].

N-3 PUFA, such as DHA, have important structural and functional roles in the brain, with established clinical benefits for supporting brain development and cognitive function throughout life. Data from animal models of TBI have consistently demonstrated that the injury-induced reduction in cognitive function is diminished with either preinjury or post-injury n-3 PUFA supplementation, particularly DHA. A study in humans examined the effect of differing doses of DHA on serum neurofilament light (NFL), a biomarker of axonal injury, over the course of a season of American football [27], and found that a season of American football is associated with some level of subconcussive injury that results in a measurable increase in NFL. Crucially, the authors reported that supplementation with DHA likely attenuates the elevations in serum NFL coincident with periods when American football athletes typically experience more and greater-magnitude head impacts [27].

To sum up, the treatment of concussions with nutritional supplements has been understudied. A number of animal studies show that nutritional supplements have potential for improving the effects of a brain injury, but only a few human studies have found consistent benefit. N-3 PUFA have potential for sport-related concussion treatment, but in the one human trial, those taking higher preinjury dosages had more concussions, whereas in animal studies post-injury administration was as effective as pretreatment administration. NAC demonstrated a positive short-term effect on

blast-induced injuries in soldiers if administered within 24 h, but it has not yet been studied in athletes. Vitamins D, C and E have potential efficacy if taken preinjury in people with low serum levels. Current human trials on nicotinamide ribose, melatonin and branched-chain amino acids may soon provide stronger evidence for using these supplements to reduce the impact of concussion in athletes [28].

## 5. Future directions

Stressful events are associated with significant increases in plasma aromatic amino acids (AAA), i.e. phenylalanine (Phe), tryptophan (Trp) and tyrosine (Tyr), and significant decreases in branched-chain amino acids (BCAA), i.e. valine (Val), leucine (Leu) and isoleucine (Ile). BCAAs serve as the major source of nitrogen for producing glutamine in the brain. They also influence the synthesis of serotonin, dopamine, and norepinephrine [17]. In addition, since AAA and BCAA compete for the same amino acid transporter within the blood-brain barrier, a reduction in plasma BCAA levels further increases cerebral AAA uptake. Sustained cerebral AAA uptake with subsequent increased synthesis of excitatory AA could promote excessive neuronal excitation, which in turn would facilitate metabolic impairment. A study has reported decreased levels of all three BCAAs in patients with mild TBI relative to healthy volunteers [17]. Studies in animals and humans supplemented with BCAAs after moderate–severe TBI [29–31] have observed improved cognitive outcome. However, a recent study reports that increased plasma levels of isoleucine and leucine were associated with increased intracranial pressure and decreased cerebral oxygen consumption [19]. These are valuable results, but the study did not determine whether sport-related concussion alters BCAA and AAA metabolism and whether the extent of any alterations is related to injury severity and return-to-play delay. The answers to these questions are a prerequisite for any AA supplementation strategy for functional action on the brain in concussed athletes.

Previous research suggests that lactate, rather than glucose, may be the preferred fuel for neuronal metabolism [32]. The study thus went on to evaluate the effect of lactate on global brain glucose uptake in euglycemic human subjects, and found that whole-brain rate of glucose uptake was significantly 17% reduced during lactate infusion [32]. Using voltage-sensitive dye imaging and brain activation by sensory stimulation in the anesthetised rat, Wyss et al. [33] investigated several aspects of cerebral lactate metabolism and observed that neuronal activity was maintained in the presence of lactate as primary energy source. The loss of the voltage-sensitive dye signal found during severe insulin-induced hypoglycemia was completely prevented by lactate infusion. Lactate therefore seems to have a direct neuroprotective effect. The study further demonstrated that the brain readily oxidises lactate in an activity-dependent manner. Finally, the data showed a lactate concentration-dependent reduction of cerebral glucose utilisation during experimentally-increased plasma lactate levels [33]. A previous study using labelled glucose and lactate showed a massive mobilisation of lactate from corporeal (skeletal muscle, skin, and other) glycogen reserves in TBI patients [32]. By tracking the incorporation of the lactate tracer, the authors found that gluconeogenesis from lactate accounted for most of the whole-body glucose rate in TBI patients [32]. These findings warrant further investigation into the advantages of using inorganic and organic lactate salts in sport-related concussion.

Gastrointestinal dysfunction is one of several complications in TBI patients. TBI can result in increased intestinal permeability and structural and functional damage of the gastrointestinal tract. Consequently, there is evidence that intestinal bacteria are directly involved in the course of TBI. In addition, TBI was found to profoundly modify gut microbiota homeostasis, and could thus contribute to a bacterial imbalance, called dysbiosis [34]. The gut microbiota is an important internal environment factor that regulates the bidirectional communication underlying the gut-brain axis [35,36]. A recent study explored the neuroprotective effects of *Clostridium butyricum* (Cb) on brain damage in a mouse model of TBI [37]. Cb is a butyrate-producing probiotic and an effective agent known for its effects on intestinal bacteria-related diarrhea. This work demonstrated that Cb treatment effectively improved neurological deficits, brain edema, and blood-brain barrier impairment in TBI mice. Cb treatment could lead to a decrease in neuronal apoptosis and help improve colonic inflammation and gut barrier impairment [37]. Gut microbiota is therefore an important factor in TBI recovery, which points to a potential benefit of regular use of probiotics and prebiotics in TBI patients. These nutrients, consumed either in the form of a controlled and enriched diet or through dietary supplements, represent future solutions for preventing the risk of concussion and limiting its neurological consequences in athletes, especially those practicing contact sports.

## 6. Conclusion

The storm of events following sport-related concussion results in a profoundly reduced bioavailability of neurocritical nutrients, rendering the normal processes of homeostatic balance no longer functional. In turn, an increased susceptibly to neurological damage after concussion may be due to today's profoundly detrimental food trends, with poor dietary n-3 PUFA intakes (particularly DHA deficiencies), insufficient dietary sulfur, and overconsumption of processed foods. Additional nutritive support is thus required to fuel the body and brain following sport-related concussion. Furthermore, it is now well known that even in the absence of concussion, subconcussive impacts cause some level of detectable damage, and the combination of repetitive concussive and subconcussive impacts has the ability to cause long-term complications [29]. Such subconcussive events had also to be explored in terms of metabolic disorders and nutritional prevention and treatment. While much of the focus has been on treating sports-related concussion, there is now growing interest in protection before impact. Nutritional supplementation has emerged as a potential strategy to prevent and/or reduce the deleterious effects of sports-related concussion and subconcussive impacts. It remains vitally important to continue to teach athletes about concussion and make sure most athletes follow the diet recommendations associated with their sport of choice. It is also important to not have athletes return to play until they are back to their nutritional and metabolic baselines and have progressed through the nutritional return-to-play protocol [38]. Finally, for contact sports, supplements may play a role in concussion prevention and management, but the use of nutritional supplementation is not widely accepted or recommended at present.

### Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

### Informed consent and patient details

The authors declare that the work described does not involve patients or volunteers.

### Disclosure of interest

The authors declare that they have no competing interest.

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## Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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