

# TRANSFORMING CONCUSSION MANAGEMENT: NUTRITIONAL INTERVENTIONS FOR OPTIMIZED ACUTE CARE

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## Highlights

- Each year, 1 in 10 people suffer a concussion, with only 1% reported. Most occur from falls, assaults, and vehicle incidents (60%), while sports-related concussions account for just 14%.
  - Despite advances in concussion and TBI understanding, a gap remains in addressing the increased metabolic needs of the injured brain.
  - Emerging evidence highlights a critical window post-injury: within minutes, inflammation begins; by 1 hour, synapse density declines; at 4 hours, cytokines amplify damage; and by 6 hours, energy failure sets in.
  - Post-concussion, an energy crisis impairs glucose utilization, as well as neuroinflammation and glymphatic dysfunction, hindering toxin elimination and recovery.
  - Concussions have far reaching consequences involving multiple body systems, including gastrointestinal, musculoskeletal, visual, cardiac, cognitive-behavioral, hormonal, circadian rhythms disruption, sleep, and the integrity of the blood-brain barrier.
  - Our novel acute concussion intervention consists of scientifically proven nutrients that target the three key elements of brain dysfunction post-concussion: energy, inflammation, and toxin elimination.
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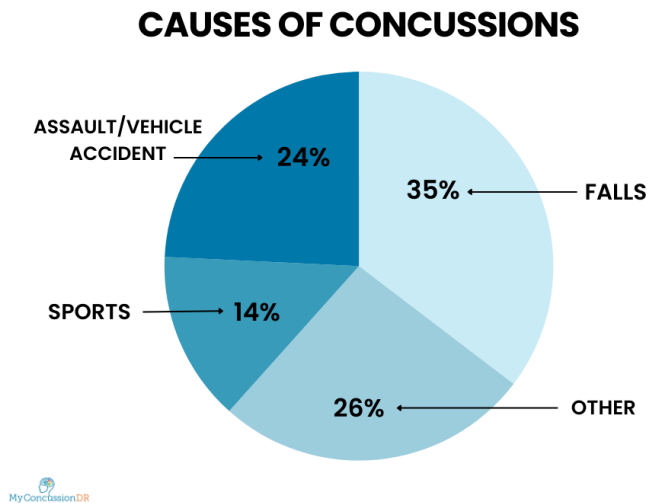
## INTRODUCTION

Every year, up to 60 million people suffer from traumatic brain injuries, including concussions, leading to staggering numbers: 27.16 million new cases, 49 million living with ongoing trauma, and a devastating 7 million years lost to disability globally (119).

Shockingly, only 1% of all suspected concussions are reported (1). The vast majority of reported concussions occur outside of sports, with falls, assaults, and motor vehicle incidents combined responsible for the majority, accounting for more than 60% of cases (1). In contrast,

sports-related concussions make up only a small fraction, around 14% (2). The consequences of these unreported and unaddressed concussions are dire on both an individual and global scale. According to a comprehensive Canadian study that followed 285 concussion patients using international sport concussion criteria, fewer than one-third of individuals with concussions fully recovered without intervention (3). Additionally, those who experienced symptoms for more than three years showed no signs of further recovery. While sports concussions are highly visible, it is essential to recognize that concussions can happen to anyone, anywhere.

It is clear in current research that dysfunction post-concussion is not limited to the brain; rather, concussions have a profound impact on multiple body systems, often leading to long-term health issues (4). These chronic sequelae cause severe long-term impacts, including cognitive impairments affecting academic/life performance, cardiac dysregulation, gastrointestinal dysfunction, hormonal dysregulation, decreased performance capacity in sports and other activities, mood changes including anxiety and depression often leading to interpersonal conflict, and neurodegenerative disease including dementia, Alzheimer’s and encephalopathy (5,6). Each concussion adds to the damage from previous ones, making the impact worse over time (120). This might explain why even a mild head injury can lead to long-term adverse effects, especially if there have been previous untreated or asymptomatic traumas. Emerging evidence suggests that a critical window may exist in the early hours to days post-injury for targeted metabolic intervention; immediate post-injury metabolic support may be helpful to prevent extensive damage and lessen the time to recovery.



## BACKGROUND

### The Vital Critical Window

Our understanding of the importance of the critical window of the early hours to days following concussion continues to expand. With a lack of robust studies in this arena to date, experts in the field advocate for “a logical application of science to the problem of concussion or a TBI”. In his 2020 seminal book *Concussion Rescue*, Dr. Kabran Chapek from Amen Clinics asks “what if we could immediately do something that increases the rate of recovery from traumatic brain injury, similar to how we routinely treat a sprained ankle with rest, ice, compression, and

elevation?" Dr. Chapek advocates for a "TBI First Aid Kit", including essential nutrients to support brain recovery, to be put to use within the first 24 hours post injury and continued for at least 7 days (72). His extensive clinical experience, and that of Amen Clinics, with TBI and concussion support his firm belief that targeted nutrient support immediately post injury is critical to support healing of the injured brain when the mechanisms of routine daily function falter (20).

Additional new studies also point to this potential window of opportunity to optimize metabolic support in order to better promote brain healing, showing detrimental impact within minutes post-injury.

- A 2021 review article titled "The synapse in traumatic brain injury" discusses the impact of traumatic brain injury (TBI) on synaptic structures. The authors highlight that TBI leads to rapid changes in synaptic proteins and a reduction in synapse density, particularly within the first 6 hours post-injury. For instance, studies have shown a significant decrease in synaptic density in the hippocampus as quickly as 1 hour after injury, with partial recovery observed over time (123).
- A 2013 study examined soldiers who suffered combat related head injury, manifesting symptoms including headaches, confusion, memory loss, and insomnia. The study revealed that early use of N-acetyl cysteine within 4 hours of injury led to resolution of symptoms in 86% as compared to only 42% in the placebo group (21). Rodent models of TBI likewise showed that early intervention within 24 hours of injury, with acetyl-L-carnitine and citicoline respectively, demonstrated benefit in recovery (22).

In addition to the commonly known metabolic responses to physical trauma, a secondary energetic crisis often occurs. It is well accepted that the brain is in a vulnerable condition immediately post-concussion as the brain is temporarily unable to use its most readily available energy source: glucose. Immediately following a brain injury, glucose transport into the cell often becomes impaired, creating an energy deficit during which the brain is unable to perform the essential functions of maintaining membrane potentials, quelling inflammation, and removing toxins.

This leads to widespread dysfunction, most notably of synapses and astrocytes, which utilize glucose to support surrounding neurons, amongst their many roles (123). After a traumatic brain injury (TBI), astrocytes quickly enter a reactive state, with astrogliosis spreading from the injury core to more distant areas of the brain (122). Near the injury site, homeostatic astroglial proteins are downregulated, while pro-inflammatory astroglial genes become overexpressed. These changes in gene expression represent a pathological remodeling of astrocytes, which has significant adverse effects on neuronal survival and cognitive recovery. Furthermore, while the glial scar formed by reactive astrocytes initially serves to limit immune cell infiltration, it ultimately hinders axonal reconnection and impairs long-term functional recovery affecting both local and global neural networks (122).

As astrocytes struggle, their key roles in maintaining pathways of amino acid metabolism, fatty acid metabolism, ion and water homeostasis, defense against oxidative stress, and resolving inflammation all fail. In times of energy crisis, as seen immediately post concussion, ketone body formation and fatty acid oxidation are essential as alternative energy sources. Astrocytes are the only source of ketone body production in the brain as well as functioning as the main sites for fatty acid oxidation in the brain (23).

Thus, as astrocytes struggle to support neurons without access to glucose, the intake of exogenous ketones provides an accessible alternate power source. This current knowledge of brain science and the role of astrocytes supports Dr Chapek's focus on "a logical application of science to the problem of concussion or a TBI", leading to the obvious question: How can we better support the recovery of faltering brain mechanisms immediately post concussion (20)? Resolution of the immediate post injury energy crisis appears to be a crucial first step .

Inflammation escalates in the brain post-injury as a normal response to tissue damage (12). In normal circumstances, the body has mechanisms to resolve inflammation, including producing anti-inflammatory cytokines and mobilizing key immune cells. With glucose utilization impaired post-brain injury, these mechanisms that guide the resolution of inflammation are impaired. Further, cells typically involved in neuronal protection, such as astrocytes and microglia, shift to create pro-inflammatory cytokine mediators such as IL-6, IL-17, TNF- $\alpha$ , and IFN- $\gamma$ , creating a vicious cycle of escalating neuroinflammation (7,11,12). Short-term consequences include the high likelihood of secondary injury with "neural priming" setting the stage for more severe damage with a second head injury (12). Over time, this may result in chronic neurodegeneration, dementia, Alzheimer's, and encephalopathy (8,9,10). Application of current brain science suggests that targeted nutrients to quiet inflammation may be helpful in optimizing brain recovery post injury (20).

Immediately post concussion, damage to the blood brain barrier and cellular structures allow influx of toxins and inflammatory proteins, including damaged tissue, into the brain. Researchers at the Nedergaard Lab at the University of Rochester Medical Center, have delineated that post-TBI:

*"Cell membranes and blood vessels rupture, spilling cytotoxic and inflammatory agents into the extracellular space and disrupting the blood supply, while blood-brain barrier breakdown leads to the influx of unfiltered blood born constituents, shutting down regular cellular metabolism."* (16).

The brain's ability to detoxify requires an effective glymphatic system to clear waste and toxins during sleep, essential for recovery (13,14). In the absence of an accessible energy source,

detoxification systems fail, allowing toxins and damaged tissue to remain in the brain, further augmenting the inflammatory response (15).

In addition to support for energy production and resolution of inflammation, application of current brain science directs support for both cellular and glymphatic detoxification pathways in order to optimize outcomes. This is supported by studies of the impact of key nutrients for detoxification in TBI recovery (24).

In summary, lacking robust clinical studies on acute interventions to date, understanding of current brain science guides new support strategies for hindered brain metabolism post injury targeting energy, inflammation, and detoxification.

## **Current Recovery Strategies**

The cornerstone of recovery recommendations has centered on “brain rest” for many decades. According to the National Federation of State High School Associations (NFHS) and the Sports Medicine Advisory Committee (SMAC), the number one priority for concussion recovery is simple: rest (17). Their suggested guide for concussion management in sports claims that “The first step in recovering from a concussion is rest. Rest is essential to help the brain heal.” (17) Sources like Johns Hopkins Medicine and the University of Michigan Health & Medicine publicly recommend and concur that full rest is preeminent for concussion treatment and recovery. “In the first one to two days after suffering a concussion, near complete rest is important.” (18)

While traditional recovery recommendations have focused on 'brain rest' and reduction of neurostimulating activity until symptoms subsided, emerging literature now supports a return to exercise early in the course of mild TBI recovery as beneficial to the recovery timeline (25, 26, 27, 28).

Recent guidelines also emphasize the importance of cognitive and physical rehabilitation. The CDC submitted a report to Congress entitled *Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation*, writing that TBI rehabilitation involves cognitive and physical therapies (19). Cognitive rehabilitation addresses cognitive deficits (learning, comprehension) and behavior, while physical rehabilitation focuses on improving mobility and ocular movement coordination.

These advancements in post concussion care, while leading to improved outcomes, continue to leave a gap in metabolic support. Emerging evidence suggests that metabolic interventions during the early post-injury period can complement these approaches. More research is clearly indicated, as the vulnerable window immediately following a concussion remains a potential opportunity where metabolic intervention could speed the brain in return to full function. The keys to a return to balance are the restoration of accessible energy for the brain, the resolution of inflammation, and the effective removal of toxins. Thus, a comprehensive treatment plan should integrate rest followed by a guided return to exercise early in the course of mild TBI recovery, cognitive and physical rehabilitation, as well as metabolic support.

## The Consequences of Missed Interventions

Each year, about 1.4 million US citizens visit emergency rooms for traumatic brain injuries (29). Despite the most current protocols, about 50% of people with TBI will experience further decline



in their daily lives or die within 5 years of their injury (30). Research published in the Journal of Head Trauma Rehabilitation demonstrated that at 10 years post-injury, the most common comorbidities developing post-brain injury, in order, were back pain, depression, hypertension, anxiety, fractures, elevated cholesterol, sleep disorders, panic attacks, osteoarthritis, and diabetes (31). These disruptions can exacerbate symptoms and hinder recovery, illustrating the far-reaching consequences of brain injuries. These consequences involve multiple body systems, including gastrointestinal, musculoskeletal, visual, cardiac, cognitive-behavioral, hormonal, circadian rhythms disruption, sleep, and the integrity of the blood-brain barrier.

## System Effects

### *Gastrointestinal*

Numerous studies demonstrate a shift in gastrointestinal function following a traumatic brain injury (TBI). These shifts are felt both due to altered composition of the intestinal microbiome (dysbiosis) as well as increased permeability of the intestinal barrier, also known as “leaky gut.” A 2023 study out of Loyola University showed that individuals after TBI have increased levels of the potentially pathogenic bacteria *Bilophila Wadsworthia* and decreased levels of bile acids in their feces and plasma (32). These changes can foster maldigestion, intestinal dysfunction, and neuroinflammation, disrupting the balance of the bi-directional gut-brain axis. This has central nervous system (CNS) implications as at least 80% of serotonin is created in the intestinal tract; thus, neurotransmitter production is disrupted, impairing CNS homeostasis (32). Further, escalating inflammation can worsen CNS injury with antiinflammatory pathways impaired post-TBI (33).

In addition to shifts in the microbiome, increased intestinal permeability can disrupt the gut-brain axis after TBI, as demonstrated first in studies of concussed rats (34).

Studies of the significance of intestinal permeability following TBI in humans are growing in number. A 2024 study in the International Journal of Molecular Science studied military “breachers” exposed to repetitive low-level blasts, many with symptoms of mild traumatic brain

injury. Biomarkers of intestinal permeability were assessed pre-, post, and the next day after the blast and were found to be elevated (35).

Prior to the above study, human clinical data on mucosal barrier function following TBI was limited to studies of ICU patients. A 1998 study in the *Journal of Trauma* assessed gut permeability using lactulose/mannitol absorption ratios in TBI patients and detected impaired barrier function 4 days after injury; permeability was correlated with disease severity and long-term prognosis (36).

There is general consensus based on multiple studies that intestinal permeability has a clear correlation with multiple forms of autoimmunity, with growing evidence of links to psychiatric disorders as well as neurodegenerative diseases, including Parkinson's disease and Alzheimer's. Thus, attention to repairing intestinal barrier integrity after TBI appears to be a vital component of a treatment plan aimed at prevention of these long-term chronic diseases.

### *Visual*

Traumatic brain injury (TBI) can result in a variety of visual issues affecting different parts of the optic system (37). Oculomotor behavior is typically categorized into convergence issues, fixations, smooth pursuits, and saccades (38). TBI, regardless of severity, is often associated with changes in all four categories, possibly resulting in significant impairment. This impairment translates to issues with response inhibition, short-term spatial memory, motor-sequence programming, visuospatial processing, and visual attention (39). Literature trends suggest that impaired eye movement function correlates more strongly with increased post-concussive symptom loads and difficulties in daily living activities (40). This can manifest as dizziness with movement and car sickness.

### *Cardiac*

Traumatic brain injury causes a surge in catecholamines, which are hormones and neurotransmitters that regulate the fight-or-flight reaction, affecting cardiac cell receptors and leading to a systemic inflammatory response (41, 42). This response creates cellular dysfunction, which damages the brain and peripheral organs, including the heart. Among the complications of TBI, cardiac injury is a frequent occurrence, affecting approximately 25–35% of patients with TBI (42). The most common heart problems in people with TBI are a higher risk for developing chronic cardiovascular disease and irregular heart rhythms (42, 43). These issues occur up to 5 to 10 times more often in individuals with TBI history than in the general adult population (43).

### *Musculoskeletal*

A recent meta-analysis has highlighted a significant increase in the risk of subsequent injuries following an initial concussion. Specifically, individuals who have sustained a concussion have a 2.5 times greater risk of experiencing a subsequent musculoskeletal injury or a second

concussion (44). This heightened risk is consistent across different levels of athletic competition, including professional, collegiate, and recreational athletes, as confirmed by another comprehensive review. Notably, the increased risk of injury remains present for up to 3 years following a concussion, well beyond the typical timeframe for concussion symptom resolution (44).

Recent studies continue to provide valuable insight into how traumatic brain injury can significantly disrupt molecular pathways, leading to changes in bone formation and remodeling possibly contributed to by parathyroid disruption. TBI has been linked to the abnormal development of bone tissue and increased callus formation (45). These abnormalities are primarily due to enhanced vascularization and the overactivation of systemic factors. Additionally, TBI can disrupt endocrine factors and neuropeptides, which may adversely affect bone health and metabolism.

### *Blood-Brain Barrier*

When a TBI is sustained, there is an immediate and direct impact on the blood-brain barrier, which may lead to detrimental long-term effects. Blood-brain barrier dysfunction, including activation of aquaporin-4 water channels, allows toxic materials usually excluded to enter the brain, such as bacterial lipopolysaccharide, environmental toxins, immune cells, and serum proteins, exacerbating the inflammatory response already set in motion by tissue damage. The compromise of the blood-brain barrier acts as a catalyst (46, 47) in the inflammatory cascade post injury.

### *Cognitive-behavioral*

Cognitive effects post-concussion are frequent, with a cross-sectional study following over 8,000 high school and college athletes finding the likelihood of developing Attention Deficit Hyperactivity Disorder (ADHD) or a Learning Disability (LD) were 2.93 and 2.0 times higher in those with a history of concussions (48).

Individuals who have sustained a traumatic brain injury (TBI), regardless of the injury's severity, are also more prone to developing chronic mood disorders and psychiatric conditions. These can include anger, depression, and anxiety, as well as post-traumatic stress disorder (PTSD). Depression and anxiety were noted in up to 30% of individuals as long-term developments post-injury (49). This is due not only in part to the psychological trauma associated with the incident, but also with neurotransmitter disruption and brain inflammation both acting as compounding factors.

Studies have indicated that hippocampal damage can be a significant indicator of mood disorders in patients assessed after a TBI. This damage leads to both short-term and long-term deficits in working, declarative, and episodic memory. Individuals with moderate to severe head injuries were found to have considerably smaller hippocampal volumes compared to those with

mild TBI. Additionally, patients who developed mood disorders exhibited notably reduced hippocampal volumes (50).

A comprehensive study on the cognitive effects of TBI demonstrated that individuals with a history of TBI performed worse on tasks involving executive function, attention, and memory compared to control groups (51). This research highlighted that cognitive impairments are prevalent among TBI survivors, affecting their daily functioning and quality of life.

Suicide, specifically the time-to-suicide, was thoroughly studied among 860,892 soldiers, including 108,785 who had experienced at least one documented TBI. The increase in mental health diagnoses from before to after TBI was significantly greater compared to those without a TBI history (51). Additionally, the time-to-suicide was 16.7% faster for soldiers with a TBI history than for those without.

Following a traumatic brain injury, anger and the ability to empathize are frequently reported concerns. From irritability to outbursts, up to one-third of patients report having negative behavioral symptoms following a concussion. Compared to the control participants, those with TBI reported a decreased ability to empathize emotionally, often associated with anger and low motivation (52).

These cognitive and emotional challenges also have a significant impact on caregivers. Caregivers of individuals with TBI often experience high levels of stress and burden, as they must manage not only the physical needs of the patient but also the psychological and behavioral changes (53). The demands of caregiving can lead to feelings of burnout, anxiety, and depression among caregivers. Research has shown that caregivers of TBI patients report lower quality of life and higher levels of psychological distress compared to caregivers of individuals with other chronic conditions (54).

### *Hormonal*

TBI is associated with hormonal disruption on multiple levels (55).

A 2024 review in *Brain and Spine* highlighted several post-TBI neuroendocrine studies, identifying cortisol as the most frequently elevated hormone, peaking within 24 hours of injury (56). Heightened levels of cortisol can lead to a maladaptive inflammatory response, perpetuating dysfunction of both the blood-brain barrier and neuronal cells, leading to a plethora of negative symptoms (57). After the initial cortisol spike, long-term cortisol dysregulation amongst other adrenal hormones is followed. Adrenal dysfunction is associated with fatigue, inadequate stress response, decreased memory, social issues, and mood or emotional disorders (58).

In addition to the disrupted adrenal axis, a broad range of pituitary hormone deficiencies are noted in one-third of adults and children post-TBI (58). As the pituitary gland produces

hormones that stimulate the gonads to produce estrogen, progesterone, and testosterone, it is not startling that studies confirm deficiencies in these reproductive hormones post-TBI (59). In 36 to 100% of males with severe TBI, investigation of luteinizing hormone (LH) and testosterone levels has identified a high incidence of low testosterone levels (60). Pituitary dysfunction following a traumatic brain injury, which can include conditions like hypopituitarism, hypothyroidism, and hypogonadism, can impact executive function, concentration, problem-solving ability, memory, and speech (61).

### *Sleep*

Fatigue, insomnia, attentional deficits, and impaired cognitive function are symptoms of dysregulated sleep cycles following a traumatic brain injury, significantly reducing quality of life. (62). Affecting 30–70% of individuals, these symptoms can be the result of various types of head trauma, with symptom expression impacted by the location and severity of the injury. Brain injury is often associated with disruption in natural circadian rhythms which function to regulate sleep/wake cycles via neuroendocrine hormonal pathways. This can manifest as either insomnia or hypersomnia.

Traumatic brain injury patients with sleep disturbances have been found to have longer inpatient hospital stays, higher cost of rehabilitation, and higher rates of functional disability (63). Sleep disturbance post brain injury can also be impacted by pain elsewhere in the body, medications, and depression, much more common in persons with traumatic brain injury than in the general population (49).

## **DETAILED DESCRIPTION**

### **Progress and Gaps in Concussion Care**

The landscape of traumatic brain injury (TBI) research is rapidly expanding, shedding light on the intricate nature of its diagnosis and understanding of its far-reaching systemic effects. There is a surge in the development of assessment protocols, as well as effective musculoskeletal, visual, and cognitive rehabilitation protocols. However, a significant gap exists in current multifaceted rehabilitation approaches in addressing acute prevention of the myriad metabolic impacts leading to far-reaching systemic consequences. Amidst this evolving understanding, new methodologies are being explored to enhance assessment comprehensiveness. These include qEEG biomarkers or electrical signals recorded from the brain that can provide valuable insights into brain function and dysfunction. qEEG biomarkers have shown promise in assessing the severity and prognosis of traumatic brain injury (TBI) (65). Research indicates that quantitative EEG (QEEG) can identify, confirm, measure, and localize brain injury (65). These biomarkers help monitor cognitive function and detect abnormalities over time. In addition, various blood tests are being investigated as possible TBI biomarkers.

Eye-movement tracking devices are becoming more standardized and better understood for their value in assessing the state of the visual and autonomic nervous system (66). These advanced assessment methods offer a more detailed and holistic view of traumatic brain injuries. By using objective measurements, standardized procedures, and multi-faceted evaluation tools, clinicians can more accurately determine the severity and progression of concussions. This comprehensive approach helps understand the long-term effects of brain injuries and supports the development of more effective treatment and rehabilitation plans.

In addition to optimizing assessment, ongoing research continues to inform and update treatment protocols. At the 6th International Conference on Concussion in Sport in Amsterdam in 2022, guidelines were updated with recommendations and protocols to standardize the assessment and management of concussions (67). These guidelines address various aspects of care, including initial evaluation, symptom monitoring, return-to-play criteria, and long-term management strategies. By providing a structured framework for assessment and treatment, the Amsterdam guidelines help ensure consistency and quality of care across different healthcare settings.

The 2024 National Athletic Trainers Association (NATA) protocols for concussion management mark a significant step forward by promoting a more comprehensive approach to care (67). They now recommend early light exercise to enhance recovery, moving away from complete rest based on new evidence that physical activity aids brain healing. These protocols adopt a biopsychosocial model, integrating physical, psychological, and social factors, thus ensuring personalized treatment strategies that address mental health and social support needs.

Educational initiatives have been strengthened, aiming to equip athletes, coaches, parents, and school administrators with thorough concussion knowledge to improve prevention, recognition, and management. The protocols also emphasize multidimensional assessments, using cognitive tests, pre-competition qEEGs, and visual/vestibular screenings for tailored treatment plans.

Despite advancements in assessment, the treatment landscape for TBIs remains relatively sparse, with only a few methods available to address the complex acute and chronic treatment needs of individuals affected by concussions. Efforts to develop a simplified, comprehensive approach are underway, driven by the growing understanding of the multifaceted nature of concussions and their impact on overall health and well-being.

One notable treatment approach is Vizstim, which promotes cognitive rehabilitation through a series of exercises designed to engage both the musculoskeletal and visual systems (68). By targeting these specific areas, Vizstim aims to improve cognitive efficiency over the long term.

Other impactful treatment modalities with increasing support in the scientific literature include hyperbaric oxygen, Neurofeedback, as well as vagal nerve stimulation and retraining (70, 71, 72).

Multiple sources are now recommending targeted nutritional support for brain metabolism in the acute TBI phase, notably Dr Kabran Chapek and other experts in the field from the Amen Clinic (69). Currently, however, there is no simple, easy to administer, systems-wide approach to

address the magnitude of the brain's unique metabolic demands during this vulnerable period. Much progress remains to be made in the realm of acute metabolic system failures to bridge this gap and optimize outcomes.

## **A Comprehensive Solution: Introducing Concussion911**

In response to the growing need for enhanced concussion care, a scientifically formulated nutritional solution appears to be the most viable option to support individuals immediately and in the acute phase after a suspected head injury. This innovative approach, Concussion911, emphasizes prompt intervention, optimization of brain energy production and utilization, and consumption of essential nutrients to foster recovery. By addressing these critical needs, our easy-to-use nutritional support aims to minimize the extent of damage, accelerate the healing process, and reduce the incidence of secondary complications.

Unlike conventional methods that primarily address symptom management, Concussion911 takes a proactive stance by leveraging the brain's inherent mechanisms for healing and recovery in acute settings. Supported by robust research and expert insights, this solution offers an effective and integrative method for managing concussions, bridging the gaps in current treatment, and promoting overall well-being. Through a carefully curated blend of nutrients, including vitamins, minerals, antioxidants, and neuroprotective compounds, we aim to support the multiple known system failure points with an optimized energy source, and compounds proven to both mitigate neuroinflammation and improve detoxification via both glymphatic and systemic pathways.

### **Mitigating Neuroinflammation**

#### *Vitamin D*

Vitamin D is not only a vitamin but functions as a hormone in many body processes (74, 76) . It has broad anti-inflammatory, increased cardiac ejection volume, and neuroprotective effects, acting as an “immunomodulator” to dampen excessive immune responses (75). Vitamin D also helps to keep calcium in balance, which is important in TBI as excess calcium released in response to cellular damage fosters neuronal cell death (74, 75).

#### *Omega-3*

Omega-3 essential fatty acids have been shown to decrease the damage caused by brain injury (77, 78, 80, 81, 82). They are essential components of cell membranes, protecting cells from oxidative damage. The fatty acids EPA and DHA are both neuroprotective via multiple mechanisms, including increasing brain-derived neurotrophic factor (BDNF) (84). They are also essential in resolving inflammation via “resolvins” which act as proresolving mediators (83).

#### *N-Acetyl Cysteine (NAC)*

N-acetyl Cysteine (NAC), as a precursor to Glutathione, is a powerful antioxidant and supports detoxification. A 2013 randomized controlled trial involving 81 military personnel with artillery-blast head injuries demonstrated that those treated with oral NAC within 24 hours of injury experienced a significant improvement in symptom resolution compared to the control group. The study reported that 86% of the NAC group had complete symptom resolution compared to 42% in the placebo group (85). A 2013 study demonstrated that impaired glutathione synthesis is linked to increased risk for neurologic disease (86). Topical glutathione reduced cell death in an experimental model of TBI in mice (87).

### *Curcumin*

Curcumin, an active ingredient in turmeric, has been a well-known anti-inflammatory for centuries. In a mouse model of brain injury, curcumin was shown to decrease brain swelling following TBI and reduce interleukin-1, an inflammatory chemical released in the brain. It also decreased the activation of aquaporin-4, a water channel protein in cell membranes, including the blood-brain barrier. When activated, aquaporin-4 allows toxins to flow through to the usually well-protected brain (88). A 2022 meta-analysis revealed that curcumin, the active form in turmeric, exhibited protective effects on TBI via modulation of multiple cell signaling pathways (89). Curcumin exhibits beneficial immunomodulatory functions and protective capacities in multiple different TBI models (90, 91).

### *Vitamin C*

Further brain injury, known as “secondary injury,” is felt to be due to several mechanisms, including oxidative stress. Vitamin C becomes quickly depleted during times of critical illness, allowing the damage cascade to continue. Vitamin C is a powerful antioxidant that has been shown to improve outcomes in patients with acute TBI (24, 92).

### *Pregnenolone*

Pregnenolone is a neuroprotective and neuroactive inhibitory steroid that helps the nervous system to calm down. It has been found to be low in patients with a history of TBI. In a randomized study of 30 military veterans with mild TBI, pregnenolone has been shown to help with insomnia, irritability, and hypervigilance (all symptoms that overlap with post-concussive syndrome) (93).

## **Optimizing the Brain’s Energy Consumption**

### *Ketones*

Ketone bodies, produced in the liver as well as by brain astrocytes, are the most efficient fuel source for the brain (97, 98). Within the first 24 hours after TBI, an “energetic crisis” occurs as glucose metabolism in the brain is altered. This is followed by neuroinflammation at the site of injury that further impairs metabolism and energy production in the brain (23). Ketone bodies are naturally created in the fasting state. Studies in animals show that fasting after moderate

TBI causes increase in ketones which are associated with neuroprotection, improved mitochondrial function, decreased oxidative stress, with maintenance of cognitive function (95). Exogenous ketones can provide the brain with much needed energy in the early hours to days after concussion (96). A 2024 review in *Current Opinion in Clinical Nutrition and Metabolic Care* highlights the opportunity for incorporating ketones in a comprehensive TBI management approach (94).

### *Acetyl-L carnitine*

Acetyl-L-carnitine assists the mitochondria in the production of energy. Acetyl-L-carnitine exerts neuroprotection via anti-inflammatory effects and as well as its effects on regulation of neuronal synaptic plasticity by counteracting post-trauma excitotoxicity (99, 100). In several animal studies, it has been shown to reduce damage from TBI. In a 2010 study using a rat model of TBI, treatment with acetyl-L-carnitine during the first 24 hours after TBI improved behavioral outcomes and reduced brain lesion volume in immature rats within the first 7 days after injury (20, 22). A 2023 study, also using a rat TBI model, demonstrated that acetyl-L-carnitine treatment showed protective effects against those observed in the untreated rat TBI group (99).

### *Citicoline*

Citicoline, or CDP-choline, is a component of human metabolism as an intermediate in the synthesis of phosphatidylcholine, the main phospholipid in cellular membranes, including neuronal and glial cells. It is also a factor in the balance of the acetylcholine neurotransmitter system necessary to carry messages from the brain to the rest of the body. Citicoline has been shown to increase the incorporation and metabolism of glucose, as well to decrease lactate levels in the brain during ischemia (102, 103). Choline has shown promise in improving outcomes in patients post TBI (101, 102, 103, 104). A 2016 meta analysis of patients with head injury treated with citicoline within the first 24 hours showed increased independence in the follow up period (101). A retrospective matched pair analysis from Austria in 2018 demonstrated reduced rates of intensive care unit (ICU) mortality, in-hospital mortality, 6-month mortality, as well as of unfavorable outcomes (105).

While the largest human prospective trial of choline in TBI, the Citicoline Brain Injury Treatment Trial (COBRIT), failed to show a significant difference, there were however methodologic issues with the study. COBRIT was a double-blind randomized and placebo-controlled trial of 1296 patients with mild, moderate or severe TBI (106). The inclusion of mild, moderate and severe TBI may have limited the power of the study to detect significant differences in these populations separately. In addition, sample size was not large enough to prove an optimal odds ratio, and compliance of only 44.4% of patients having taken more than 75% of the medication further limited the study design (106). Further study is clearly indicated.

### *Magnesium*

Increasing evidence suggests that decline in Magnesium is a critical factor in acute brain injury, and that Magnesium supplementation can have beneficial impact on outcomes post brain injury

(107, 108, 109, 110, 111, 121). A 2007 rat model exhibited magnesium chloride to be effective in facilitating cognitive recovery of function following brain injury (112). A followup study by the same author, also a rat model, demonstrated that magnesium treatment was successful at attenuating cognitive and motor deficits after TBI (113). Human studies have been mixed, and as there are recently discovered variations of Magnesium chelates that can cross the blood brain barrier, including Magnesium threonate, clearly more human studies are needed.

## ***Optimizing Detoxification Pathways***

Several well studied essential nutrients for detoxification, both intracerebral and systemic, have been included in our nutrient supportive blend.

### *N-acetyl Cysteine (NAC)*

NAC, as the precursor to the “master antioxidant” Glutathione, aids the liver in detoxifying the body from potentially harmful toxins and chemicals. In the brain Glutathione is critical in detoxification of reactive oxygen and nitrogen species (114).

### *Vitamin C*

Vitamin C is a powerful antioxidant, mitigating increased reactive oxygen species and free radicals associated with tissue damage. It is an essential nutrient in system wide detoxification processes (115).

## **Additional Support**

### *Creatine*

Creatine has shown promise for attenuating symptoms of concussion, mild TBI and depression (116, 117, 118). A 2023 review of 15 articles supports the benefit of creatine in patients post TBI (118). Of note, results are only clinically significant after a month of supplementation. Creatine showed efficacy as a neuroprotective agent in battling the chronic manifestations which lead to oxidative stress and cognitive function post brain injury (118).

## **Safety Considerations**

If you feel your concussion is due to chemical induced brain injury, consult your TBI informed provider before starting this supplement and consider starting at small doses due to increased potential for unpredictable reactivity. Contraindications to Concussion911 are pregnancy, breast feeding, active cancer treatment, and blood thinning medications. As with all supplements and medications, there is individual variability in tolerance. Do not take additional Vitamin D, creatine, or omega 3's while using Concussion911. Consult with your doctor if you are taking pharmaceutical medications in order to rule out potential interactions.

## **CONCLUSION**

Despite huge advances in the understanding of the pathophysiology of concussion and TBI leading to better assessment and therapeutic strategies, there remains a gap in understanding and addressing the metabolic needs during the critical window of the early hours following concussion. Our targeted nutrient and nutraceutical formulation within Concussion911 addresses this opportunity for effective acute intervention to support metabolic pathways.

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