PILAWSKA, Sandra Agnieszka, BADO, Michał, GONCERZ, Michał, NOWOŚWIAT, Patrycja, BILECKI, Krzysztof, BEDNARCZYK, Paulina, MALAKA, Ewa Katarzyna, DUDA, Weronika, MUZYK, Magdalena and MAŚLANKIEWICZ, Maria. The role of supplementation in traumatic brain injury among athletes and non-athletes population. Quality in Sport. 2024;19:54097. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.19.54097
https://apcz.umk.pl/QS/article/view/54097

The journal has had 20 points in Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 06.08.2024. Revised: 19.08.2024. Accepted: 29.08.2024. Published: 31.08.2024.

The role of supplementation in traumatic brain injury among athletes and non-athletes population

Sandra Agnieszka Pilawska
The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow, Poland
https://orcid.org/0009-0005-3565-9723
Michał Bado
The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow, Poland
https://orcid.org/0009-0008-6595-6560
Michał Goncerz
Department of Anatomy - Jagiellonian University, Kopernika 12 Street, 31-034 Krakow, Poland
https://orcid.org/0009-0003-8444-6922
Patrycja Nowoświat
The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow, Poland
https://orcid.org/0009-0008-7939-6621
Krzysztof Bilecki
SP ZOZ MSWiA, Kronikarza Galla 25, 30-053 Cracow, Poland

https://orcid.org/0009-0001-8778-1422
Paulina Bednarczyk
The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow, Poland
https://orcid.org/0009-0009-3598-2490
Ewa Katarzyna Malaka
The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow, Poland
https://orcid.org/0009-0007-6746-698X
Weronika Duda
H. Klimontowicz Specialist Hospital in Gorlice, Węgierska 21, 38-300 Gorlice, Poland
https://orcid.org/0009-0007-1332-7036
Magdalena Muzyk
5th Military Clinical Hospital with Policlinic (SPZOZ) in Krakow, ul. Wrocławska 1-3, 30-901 Kraków, Poland
https://orcid.org/0009-0008-4822-5651
Maria Maślankiewicz
The University Hospital in Krakow, Jakubowskiego 2 Street, 30-688 Krakow, Poland
https://orcid.org/0009-0005-0121-411X

Abstract

Introduction: Traumatic brain injury (TBI) is one of the most common causes of death and long-term disability. The consequences following TBI can be persistent and cause life-long implications for survivors. Treatment of TBI may be complex and involve large monetary costs. The frequent injury mechanisms are traffic-related, falls, violence or sport-related accidents. Higher risk of brain injury and its complications indicate that people affected by brain trauma may benefit from the prophylactic and post-traumatic use of certain supplements both in the context of physical performance and in the event of potential injury.

Aim of the Study: This narrative review examines the current literature of the role of supplementation before and after TBI and its effects on the patient's outcome.

Materials and Methods: A comprehensive search was performed using PubMed and Google Scholar focusing on the literature published up to April 2024. The review included randomized controlled trials, meta-analyses, systematic reviews that focused on the use of creatine monohydrate, omega-3 fatty acids, magnesium and zinc in TBI and among the

general population. Data of pathophysiology and epidemiology of TBI and safety profile of supplements were involved.

Results: The evidence indicates that the role of supplementation with creatine, omega-3 PUFAs and zinc is important in mitigating secondary damage after TBI, as well as in protecting against damage if administered before injury.

Conclusion: Because of the complex and multifactorial nature of the TBI more studies are required to constitute an effective nutrition-based strategy for reducing the cognitive and behavioral deficits associated with this injury. The evidence supporting multiple dietary components to improve a patient's outcome seems strong and the cost of its implementation is low. A group of particular interest that may benefit additionally are athletes who use dietary supplementation in their daily routine.

Keywords: traumatic brain injury, creatine, omega-3 fatty acids, magnesium, zinc

Introduction

Traumatic brain injury (TBI) is one of the most common causes of death and long-term disability. In European countries the incidence rate ranges from 47.3 to 849 per 100.000 per year for all ages (Brazinova et al., 2021). The consequences following TBI can be persistent and cause life-long implications for survivors (Tagliaferri et al., 2005). Treatment of TBI may be complex and involve large monetary costs (Tagliaferri et al., 2005). The frequent injury mechanisms are traffic-related, falls, violence or sport-related accidents (Brazinova et al., 2021). TBI pathophysiology consists of two types of damage - primary and secondary. The first type is caused by the external force itself and includes increases in intracranial pressure, edema, hemorrhages and strains of the neural and vascular tissue leading to axonal injury (Mira et al., 2021; Nakagawa et al., 2011; Young et al., 2015). Secondary damage refers to molecular and cellular consequences which occur in hours and days after incident and causes further axonal degeneration and demyelination, oxidative stress, mitochondrial and synaptic damage, neuroinflammation and protein aggregation. What is important - the secondary damage is responsible for the persistence of symptoms and increased vulnerability to new trauma or neurodegenerative disorders of the brain (Mira et al., 2021). TBI should be conceptualized as a chronic health condition which can have lifelong effects on health and wellbeing such as seizures, neurodegenerative disease, emotional difficulties, cognitive impairment and functional limitations (Wilson et al., 2017).

Concussion due to sport-related TBI in contact sports occurs with frequency from 1.6 to 3.0 millions cases annually in the United States (Ianof et al., 2014). However, many sport-related TBIs are unrecognized and unreported. Repetitive head injuries may occur in sports like football, soccer, rugby, hockey or martial arts (e.g. boxing or wrestling) as well as high-velocity sports such as cycling, motor racing, equestrian sports, rodeo, skiing and roller skating (Ianof et al., 2014; 8McKee et al., 2009). Lehman EJ et al. showed that among former professional football players, who are exposed to repetitive mild TBI, the neurodegenerative mortality is 3 times higher than that of the general US population (Lehman et al., 2012). Another study suggests that there is a possible link between recurrent sport-related concussion and increased risk of clinical depression (Guskiewicz et al., 2007). Next group exposed to TBI, especially mild TBI or concussion, is the military service (Lehman et al., 2012; Helmick et al., 2015). Higher risk of brain injury and its complications indicate that these populations may benefit from the prophylactic use of certain supplements both in the context of physical performance and in the event of potential injury.

Many pre-clinical and clinical studies suggest that nutritional interventions may be implemented to prevent unwanted events caused by the secondary damage of TBI. The aim of this review is to highlight the role of supplementation before and after TBI and its effects on the patient's outcome.

Creatine monohydrate

Creatine monohydrate is a well known supplement among athletes as well as amateur sportsmen and sportswomen (Butts et al., 2018). Its intake, combined with physical training, improves performance and increases body mass both in young and older adults (Branch 2003; Chilibeck et al., 2017). Creatine supplementation may also have beneficial effects on cognitive functions in healthy individuals, especially elderly (Prokopidis et al., 2023; Avgerinos et al., 2018; Dolan et al., 2018). Recent studies demonstrated the efficacy of chronic creatine ingestion in post-COVID-19 fatigue syndrome by reducing general fatigue after 3 months of intake compared to baseline values ($p = 0.04$), and significantly improved scores for several post-COVID-19 fatigue syndrome-related symptoms (e.g., ageusia, breathing difficulties, body aches, headache, and difficulties concentrating) at 6-month follow-up ($p < 0.05$) (Slankamenac et al., 2023; Slankamenac et al., 2024). Longitudinal studies showed safety of short-, medium- and long-term creatine consumption for the kidney and liver in healthy subjects (Poortmans and Francaux, 2000; Poortmans et al., 1997;

Poortmans and Francaux, 1999; Kreider et al., 2003; Poortmans et al., 2005; Gualano et al., 2010; Neves et al., 2011). Moreover, there is no risk for groups prone to kidney dysfunction like elderly people (Neves et al., 2011) or type 2 diabetic patients (Gualano et al., 2011).

Sullivan et al. showed in animal models that chronic administration of creatine may ameliorate the extent of cortical damage after experimental TBI. Neuroprotective effects may result from maintaining mitochondrial membrane potentials, reducing free radical production and lowering levels of intramitochondrial Ca2+ (Sullivan et al., 2000). In further studies, creatine-fed animals after experimental TBI presented significantly lower levels of both free fatty acids and lactic acid than control group, which are markers of secondary cellular injury following TBI (Scheff and Dhillon, 2004). These results support the idea that creatine-enriched diet can provide neuroprotection related to mitochondrial integrity.

One of the major complications after the TBI may be the post-traumatic seizures (PTS) in the early stage after injury and developing post-traumatic epilepsy thereafter (Lucke-Wold et al., 2015). Given previous studies, it would seem that creatine supply may have an impact on preventing these conditions. Although creatine reduces oxidative stress markers and stabilizes mitochondrial membrane potentials, it still does not protect against seizures in the first week after TBI (Saraiva et al., 2012). Despite the administration of creatine within 30 min after TBI, animals tested with subconvulsive dose of pentylenetetrazol (PTZ), 4 days after TBI, had lower latency and longer duration for tonic–clonic seizures. Surprisingly, another study conducted by Gerbatin et al. showed that delayed creatine supplementation may be beneficial in this field (Gerbatin et al., 2019). This time rats from the experimental group were fed creatine from one week after TBI. The study demonstrated that delayed and chronic creatine supplementation promotes a protective and sustained effect against susceptibility to EEG and behavioral seizures induced by PTZ after TBI. Moreover, the protective effect of creatine against brain excitability following TBI was observed. Creatine administration was associated with the reduction in cell loss including GABAergic neurons followed by the regulation of parameters involved in the GABAergic function (Gerbatin et al., 2019).

Similar research was conducted with human individuals. Sakellaris et al. performed a pilot study involving 39 children and adolescents with TBI which showed that creatine administration improved results in several parameters, including duration of post-traumatic amnesia, duration of intubation, intensive care unit stay, disability, good recovery, self care, communication, locomotion, sociability, personality/behavior and neurophysical, and cognitive function. Significant improvement was recorded in the categories of cognitive ($p <$

0.001), personality/behavior ($p < 0.001$), self care ($p = 0.029$), and communication ($p = 0.018$) aspects in all patients. Additionally, no side effects were seen after creatine intake (Sakellaris et al., 2006; Sakellaris et al., 2008).

Available literature on creatine supplementation suggests that this compound may be useful in alleviating secondary damage after TBI as well as in protecting against damage if administered pre-injury. Moreover, in populations at high risk for mild TBI such as athletes and military personnel, who are already taking the compound to some degree, the possible benefits are of particular interest (Ainsley Dean et al., 2017). However, more clinical studies are required in this field as well as protocols for creatine administration.

Omega-3 polyunsaturated fatty acids (omega-3 PUFAs)

Omega-3 polyunsaturated fatty acids (omega-3 PUFAs) seem to be very useful supplements for a huge range of the population like athletes, elderly with sarcopenia and patients with cardiovascular and inflammatory diseases (Schubert et al., 2008; Cottin et al., 2011; Smith et al., 2015; Black et al., 2018). In the older population, six months of supplementation (3.36 g per day) brought benefits in the form of an increased muscle mass (+3.6%) and strength (+4%) (Smith et al., 2015). In another study seven days of 3 g per day omega-3 PUFA supplementation decreased soreness after eccentric exercise (Jouris et al., 2011). Positive results in muscle recovery and training adaptation were reported in similar studies (Lembke et al., 2014; Corder et al., 2016; Tsuchiya et al., 2016). Omega-3 PUFAs supplementation seems to be beneficial also for professional athletes. Group of professional Rugby Union players who digested 1546 mg of omega-3 PUFAs twice a day for 5 weeks resulted in a moderate beneficial effect on lower body muscle soreness, better maintenance of countermovement jump performance and moderate reduction in fatigue during pre-season training (Black et al., 2018).

In addition to these benefits, omega-3 PUFAs supplementation may also carry benefits for patients with TBI. Fish oil supplementation in a rat model of multiple mild TBI showed that pre-injury intake improves recovery of body weight and provides a small improvement in cognitive performance (Wang et al., 2013). Another study with rodents suggests that omega-3 PUFA supplementation attenuates the inflammatory response by modulating microglial polarization, leading to neuroprotective effects following experimental traumatic brain injury (Chen et al., 2018). Diet supplemented with omega-3 PUFAs before TBI can provide protection against behavioral dysfunction, hippocampal neuronal loss, inflammation, loss of

myelination and impulse conductivity, reduced plasticity and impaired learning ability which are consequences of injury (Wu et al., 2004; Pu et al., 2013; Mills et al., 2011; Begum et al., 2014). In a study conducted on the human population (n = 40), a DHA (docosahexaenoic acid, an omega-3 fatty acid) group of children (mean age 16 years) took 2000 mg of DHA per day after sport-related concussion for 12 weeks. Compared to the PLACEBO group, subjects in the DHA group were symptom-free 4 days earlier (16.1 vs. 20.9 days, p=0.082) and were cleared to begin a return to play progression (21.4 vs. 23.4 days, p=0.115) sooner. One nontoxic outcome (excessive burping) was observed, however follow up was poor in the DHA group (50%, n = 10) when compared to the placebo during the 12 weeks. The reason for poor follow-up on week 12 was not specifically identified by authors. This may have been due to faster symptom relief, and patients were allowed to return to play within 4 weeks, resulting in no further follow-up at week 12. (Miller et al., 2019).

Whether omega-3 PUFAs are effective mainly as a prophylactic treatment should be considered. To further evaluate the therapeutic potential of omega-3 PUFA in TBI, additional studies evaluating the efficacy of this supplement with delayed administration in secondary damage of TBI are warranted. While this may be the limitation in the general population, in populations exposed to TBI such as athletes or military personnel, omega-3 PUFA can provide significant benefits, in physical performance and as a TBI prophylaxis, when incorporated into the diet.

Magnesium

Patients with severe head injury are at high risk of developing electrolytes disorders including hypomagnesemia (Polderman et al., 2000) which is an important determinant of outcome following TBI through its effect on secondary damage (Nayak et al., 2018). While preclinical studies in animal models have yielded promising results (Feldman wt al., 1996; Browne et al., 2004; Bareyre et al., 2000; Heath and Vink, 1999; Hoane and Barth, 2002), clinical trials have not been as optimistic. In a double-blind clinical trial reported by Temkin et al. continuous infusions of magnesium for 5 days given to patients within 8 h of moderate or severe traumatic brain injury were not neuroprotective and might even have a negative effect in the treatment of significant head injury (Temkin et al., 2007). In another prospective clinical study magnesium supply seemed to have some favorable influence on mortality and intra-operative brain swelling without any significant adverse effects (Dhandapani et al., 2008). Favorable outcome of good recovery or moderate disability at 3 months follow-up was

observed in 73.3% patients who had received MgSO4, as compared with 40% in the control group. The odds ratio (OR) was 4.13 (95% Confidence interval 1.39- 12.27) and the p value was 0.009. The number of patients dead at 1 month was 13.3% and 43.3% in MgSO4 and control groups respectively, which was statistically significant (OR 0.2, p=0.01). In contrast, Wang et al. observed that a higher initial serum magnesium level is independently associated with mortality in TBI patients (Wang et al., 2022). Patients after TBI with lower or higher levels of serum magnesium have higher mortality. The meta-analysis conducted by Lyons and Blackshaw found a lack of evidence for magnesium pharmacotherapy in severe TBI (Lyons and Blackshaw, 2018).

In conclusion, studies showed that data in this field were conflicting and significantly heterogeneous. The role of magnesium supplementation in TBI remains unclear. Further studies are required to assess usability of magnesium in TBI and protocols to determine its dosage.

Zinc

Zinc plays a variety of roles in the central nervous system. Fluctuations in its concentration may lead to neurological diseases, alterations in behavior and abnormal CNS development (Gower-Winter and Levenson, 2012). Athletes are at risk of suboptimal zinc status despite higher dietary zinc intake, which can lead to anorexia, significant loss in body weight, latent fatigue with decreased endurance and a risk of osteoporosis (Chu et al., 2018, Micheletti et al., 2001).

The subject of consideration is whether zinc in TBI is neurotoxic or neuroprotective (Levenson, 2020). It was observed that early in the post-injury course of head trauma patients serum zinc concentration is significantly reduced while urine zinc concentration is elevated (McClain wt al., 1986). Zinc supply in preclinical studies has shown promising results in animal models with TBI (Doering et al., 2010).

In a study conducted on rats, animals that were fed the zinc supplemented diet for 4 weeks after TBI showed significantly attenuated increases in adrenal weight ($p<0.05$) as well as reduced depression-like behaviors ($p<0.001$). Moreover, zinc supplementation prior to injury improved resilience such that there was significant improvements in cognitive behavior compared to injured rats fed a zinc-adequate diet ($p<0.01$) as well as there were no significant differences between supplemented and sham-operated rats in Morris water maze performance

at any point in the 10-day trial. (Cope et al., 2011) It suggests that supplementation of this mineral has protective properties in the aftermath of TBI.

In a randomized, prospective, double-blinded controlled trial of supplemental zinc versus standard zinc therapy after severe head injury Young et al. observed that zinc supplementation during the immediate postinjury period is associated with improved rate of neurologic recovery and visceral protein concentrations (Young et al., 1996). Morris and Levenson showed that use of dietary and parenteral zinc supplementation as a treatment following brain injury improved neuropsychological function (Morris and Levenson, 2013).

Zinc supplementation should be taken into consideration in TBI treatment, however it requires further studies and clinical protocols to establish a dosage regimen.

Conclusions

Creatine is a supplement with many positive effects both in terms of physical performance and cognitive functions. Its supplementation also has been proven safe. This compound may be useful in alleviating secondary damage after TBI as well as in protecting against damage if administered pre-injury.

Omega-3 PUFA supplementation improves peripheral neuromuscular function and aspects of fatigue in athletes. Its intake pre-injury improves recovery of body weight and may provide an improvement in cognitive performance and faster symptom relief after TBI.

Serum magnesium level appears to be important after head injury, but the role of magnesium supply in TBI remains unclear. In contrast, serum zinc concentration is decreased after TBI, but its administration may be beneficial in terms of neuroprotection.

The role of supplementation with creatine, omega-3 PUFAs and zinc appears to be important in mitigating secondary damage after TBI, as well as in protecting against damage if administered before injury. In populations with a higher risk of TBI of particular note are athletes who are using supplements in their daily routine to improve physical performance, as taking them pre-injury can provide a better outcome after incidence. This additional, however very important benefit of supplements intake may decrease incidence or intensity of adverse effects of TBI such as cognitive impairment, increased brain excitability, cellular damage, loss of myelination, behavioral dysfunction, depression-like behaviors, hippocampal neuronal loss and inflammation.

Because of the complex and multifactorial nature of the TBI more studies are required to constitute an effective nutrition-based strategy for reducing the cognitive and behavioral

deficits associated with this injury. The evidence supporting multiple dietary components to improve a patient's outcome seems strong and the cost of its implementation is low. The main challenge is to perform well designed clinical studies to define optimal dosage and compare single and multiple dietary components.

Disclosure

Conceptualization, Sandra Agnieszka Pilawska, and Michał Goncerz; methodology, Michał Bado, Krzysztof Bilecki; software, Patrycja Nowoświat; check, Krzysztof Bilecki, Paulina Bednarczyk and Ewa Katarzyna Malaka; formal analysis, Weronika Duda; investigation, Sandra Pilawska; resources, Magdalena Muzyk; data curation, Maria Maślankiewicz; writing - rough preparation, Sandra Agnieszka Pilawska; writing - review and editing, Michał Goncerz; visualization, Michał Bado; supervision, Paulina Bednarczyk; project administration, Patrycja Nowoświat; receiving funding, Magdalena Muzyk All authors have read and agreed with the published version of the manuscript.

Funding statement

The study did not receive special funding.

Informed Consent Statement

Not applicable.

Acknowledgments

Not applicable.

Conflict of Interest Statement

The authors report no conflict of interest.

References

Ainsley Dean PJ, Arikan G, Opitz B, Sterr A. Potential for use of creatine supplementation following mild traumatic brain injury. Concussion. 2017 Mar 21;2(2):CNC34. doi: 10.2217/cnc-2016-0016. PMID: 30202575; PMCID: PMC6094347.

Avgerinos KI, Spyrou N, Bougioukas KI, Kapogiannis D. Effects of creatine supplementation on cognitive function of healthy individuals: A systematic review of randomized controlled trials. Exp Gerontol. 2018 Jul 15;108:166-173. doi: 10.1016/j.exger.2018.04.013. Epub 2018 Apr 25. PMID: 29704637; PMCID: PMC6093191.

Bareyre FM, Saatman KE, Raghupathi R, McIntosh TK. Postinjury treatment with magnesium chloride attenuates cortical damage after traumatic brain injury in rats. J Neurotrauma. 2000 Nov;17(11):1029-39. doi: 10.1089/neu.2000.17.1029. PMID: 11101206.

Begum G, Yan HQ, Li L, Singh A, Dixon CE, Sun D. Docosahexaenoic acid reduces ER stress and abnormal protein accumulation and improves neuronal function following traumatic brain injury. J Neurosci. 2014 Mar 5;34(10):3743-55. doi: 10.1523/JNEUROSCI.2872-13.2014. PMID: 24599472; PMCID: PMC6608987.

Black KE, Witard OC, Baker D, Healey P, Lewis V, Tavares F, Christensen S, Pease T, Smith B. Adding omega-3 fatty acids to a protein-based supplement during pre-season training results in reduced muscle soreness and the better maintenance of explosive power in professional Rugby Union players. Eur J Sport Sci. 2018 Nov;18(10):1357-1367. doi: 10.1080/17461391.2018.1491626. Epub 2018 Jul 9. PMID: 29985775.

Branch, J. D. (2003). Effect of Creatine Supplementation on Body Composition and Performance: A Meta-analysis. International Journal of Sport Nutrition and Exercise Metabolism, 13(2), 198–226.doi:10.1123/ijsnem.13.2.198

Brazinova A, Rehorcikova V, Taylor MS, Buckova V, Majdan M, Psota M, Peeters W, Feigin V, Theadom A, Holkovic L, Synnot A. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. J Neurotrauma. 2021 May 15;38(10):1411-1440. doi: 10.1089/neu.2015.4126. Epub 2018 Dec 19. PMID: 26537996; PMCID: PMC8082737.

Browne KD, Leoni MJ, Iwata A, Chen XH, Smith DH. Acute treatment with MgSO4 attenuates long-term hippocampal tissue loss after brain trauma in the rat. J Neurosci Res. 2004 Sep 15;77(6):878-83. doi: 10.1002/jnr.20215. PMID: 15334605.

Butts J, Jacobs B, Silvis M. Creatine Use in Sports. Sports Health. 2018 Jan/Feb;10(1):31-34. doi: 10.1177/1941738117737248. Epub 2017 Oct 23. PMID: 29059531; PMCID: PMC5753968.

Chen X, Chen C, Fan S, Wu S, Yang F, Fang Z, Fu H, Li Y. Omega-3 polyunsaturated fatty acid attenuates the inflammatory response by modulating microglia polarization through SIRT1-mediated deacetylation of the HMGB1/NF-κB pathway following experimental traumatic brain injury. J Neuroinflammation. 2018 Apr 20;15(1):116. doi: 10.1186/s12974-018-1151-3. PMID: 29678169; PMCID: PMC5909267.

Chilibeck, P., Kaviani, M., Candow, D., & Zello, G. A. (2017). Effect of creatine supplementation during resistance training on lean tissue mass and muscular strength in older adults: a meta-analysis. Open Access Journal of Sports Medicine, Volume 8, 213–226.doi:10.2147/oajsm.s123529

Chu A, Holdaway C, Varma T, Petocz P, Samman S. Lower Serum Zinc Concentration Despite Higher Dietary Zinc Intake in Athletes: A Systematic Review and Meta-analysis. Sports Med. 2018 Feb;48(2):327-336. doi: 10.1007/s40279-017-0818-8. PMID: 29164533.

Cope EC, Morris DR, Scrimgeour AG, VanLandingham JW, Levenson CW. Zinc supplementation provides behavioral resiliency in a rat model of traumatic brain injury. Physiol Behav. 2011 Oct 24;104(5):942-7. doi: 10.1016/j.physbeh.2011.06.007. Epub 2011 Jun 16. PMID: 21699908; PMCID: PMC3506179.

Corder K.E., Newsham K.R., McDaniel J.L., Ezekiel U.R., Weiss E.P. Effects of short-term docosahexaenoic acid supplementation on markers of inflammation after eccentric strength exercise in women. J. Sports Sci. Med. 2016;15:176–183.

Cottin SC, Sanders TA, Hall WL. The differential effects of EPA and DHA on cardiovascular risk factors. Proc Nutr Soc. 2011 May;70(2):215-31. doi: 10.1017/S0029665111000061. Epub 2011 Feb 24. PMID: 21349231.

Dhandapani, S., Gupta, A., Vivekanandhan, S., Sharma, B., & Mahapatra, A. (2008). Randomized controlled trial of magnesium sulphate in severe closed traumatic brain injury. The Indian Journal of Neurotrauma, 5(1), 27–33.doi:10.1016/s0973-0508(08)80025-1

Doering P, Stoltenberg M, Penkowa M, Rungby J, Larsen A, Danscher G. Chemical blocking of zinc ions in CNS increases neuronal damage following traumatic brain injury (TBI) in mice. PLoS One. 2010 Apr 9;5(4):e10131. doi: 10.1371/journal.pone.0010131. PMID: 20396380; PMCID: PMC2852423.

Dolan, E., Gualano, B., & Rawson, E. S. (2018). Beyond muscle: the effects of creatine supplementation on brain creatine, cognitive processing, and traumatic brain injury. European Journal of Sport Science, 1–14.doi:10.1080/17461391.2018.1500644

Feldman Z, Gurevitch B, Artru AA, Oppenheim A, Shohami E, Reichenthal E, Shapira Y. Effect of magnesium given 1 hour after head trauma on brain edema and neurological outcome. J Neurosurg. 1996 Jul;85(1):131-7. doi: 10.3171/jns.1996.85.1.0131. PMID: 8683262.

Gerbatin RR, Silva LFA, Hoffmann MS, Della-Pace ID, do Nascimento PS, Kegler A, de Zorzi VN, Cunha JM, Botelho P, Neto JBT, Furian AF, Oliveira MS, Fighera MR, Royes LFF. Delayed creatine supplementation counteracts reduction of GABAergic function and protects against seizures susceptibility after traumatic brain injury in rats. Prog Neuropsychopharmacol Biol Psychiatry. 2019 Jun 8;92:328-338. doi: 10.1016/j.pnpbp.2019.02.004. Epub 2019 Feb 8. PMID: 30742861.

Gower-Winter SD, Levenson CW. Zinc in the central nervous system: From molecules to behavior. Biofactors. 2012 May-Jun;38(3):186-93. doi: 10.1002/biof.1012. Epub 2012 Mar 31. PMID: 22473811; PMCID: PMC3757551.

Gualano B, Ferreira DC, Sapienza MT, Seguro AC, Lancha AH Jr (2010) Effect of short-term high-dose creatine supplementation on measured GFR in a young man with a single kidney. Am J Kidney Dis 55(3):e7–e9. doi:10.1053/j.ajkd.2009.10.053

Gualano B, de Salles Painelli V, Roschel H, Lugaresi R, Dorea E, Artioli GG, Lima FR, da Silva ME, Cunha MR, Seguro AC, Shimizu MH, Otaduy MC, Sapienza MT, da Costa Leite C, Bonfá E, Lancha Junior AH. Creatine supplementation does not impair kidney function in type 2 diabetic patients: a randomized, double-blind, placebo-controlled, clinical trial. Eur J Appl Physiol. 2011 May;111(5):749-56. doi: 10.1007/s00421-010-1676-3. Epub 2010 Oct 26. PMID: 20976468.

Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Harding HP Jr, Matthews A, Mihalik JR, Cantu RC. Recurrent concussion and risk of depression in retired professional football players. Med Sci Sports Exerc. 2007 Jun;39(6):903-9. doi: 10.1249/mss.0b013e3180383da5. PMID: 17545878.

Heath DL, Vink R. Improved motor outcome in response to magnesium therapy received up to 24 hours after traumatic diffuse axonal brain injury in rats. J Neurosurg. 1999 Mar;90(3):504-9. doi: 10.3171/jns.1999.90.3.0504. PMID: 10067920.

Helmick KM, Spells CA, Malik SZ, Davies CA, Marion DW, Hinds SR. Traumatic brain injury in the US military: epidemiology and key clinical and research programs. Brain Imaging Behav. 2015 Sep;9(3):358-66. doi: 10.1007/s11682-015-9399-z. PMID: 25972118.

Hoane MR, Barth TM. The window of opportunity for administration of magnesium therapy following focal brain injury is 24 h but is task dependent in the rat. Physiol Behav. 2002 Jun 1;76(2):271-80. doi: 10.1016/s0031-9384(02)00714-x. PMID: 12044600.

Ianof JN, Freire FR, Calado VTG, Lacerda JR, Coelho F, Veitzman S, Schmidt MT, Machado S, Velasques B, Ribeiro P, Basile LFH, Paiva WS, Amorim R, Anghinah R. Sport-related concussions. Dement Neuropsychol. 2014 Jan-Mar;8(1):14-19. doi: 10.1590/S1980-57642014DN81000003. PMID: 29213874; PMCID: PMC5619443.

Jouris KB, McDaniel JL, Weiss EP. The Effect of Omega-3 Fatty Acid Supplementation on the Inflammatory Response to eccentric strength exercise. J Sports Sci Med. 2011 Sep 1;10(3):432-8. PMID: 24150614; PMCID: PMC3737804.

Kreider RB, Melton C, Rasmussen CJ, Greenwood M, Lancaster S, Cantler EC, Milnor P, Almada AL (2003) Long-term creatine supplementation does not significantly affect clinical markers of health in athletes. Mol Cell Biochem 244(1–2):95–104

Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. Neurology. 2012 Nov 6;79(19):1970-4. doi: 10.1212/WNL.0b013e31826daf50. Epub 2012 Sep 5. PMID: 22955124; PMCID: PMC4098841.

Lembke P., Capodice J., Hebert K., Swenson T. Influence of n-3 omega-3 PUFA (n3) index on performance and wellbeing in young adults after heavy eccentric exercise. J. Sports Sci. Med. 2014;13:151–156.

Levenson CW. Zinc and Traumatic Brain Injury: From Chelation to Supplementation. Med Sci (Basel). 2020 Aug 17;8(3):36. doi: 10.3390/medsci8030036. PMID: 32824524; PMCID: PMC7565729.

Lucke-Wold BP, Nguyen L, Turner RC, Logsdon AF, Chen YW, Smith KE, et al. Traumatic brain injury and epilepsy: underlying mechanisms leading to seizure. Seizure. 2015;33:13–23.

Lyons MWH, Blackshaw WJ. Does magnesium sulfate have a role in the management of severe traumatic brain injury in civilian and military populations? A systematic review

and meta-analysis. J R Army Med Corps. 2018 Nov;164(6):442-449. doi: 10.1136/jramc-2018-000916. Epub 2018 Apr 17. PMID: 29666199.

McClain CJ, Twyman DL, Ott LG, Rapp RP, Tibbs PA, Norton JA, Kasarskis EJ, Dempsey RJ, Young B. Serum and urine zinc response in head-injured patients. J Neurosurg. 1986 Feb;64(2):224-30. doi: 10.3171/jns.1986.64.2.0224. PMID: 3944632.

McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE, Santini VE, Lee HS, Kubilus CA, Stern RA. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J Neuropathol Exp Neurol. 2009 Jul;68(7):709-35. doi: 10.1097/NEN.0b013e3181a9d503. PMID: 19535999; PMCID: PMC2945234.

Micheletti A, Rossi R, Rufini S. Zinc status in athletes: relation to diet and exercise. Sports Med. 2001;31(8):577-82. doi: 10.2165/00007256-200131080-00002. PMID: 11475319.

Miller SM, Zynda AJ, Sabatino MJ, Ellis HB, Dimeff R. Docosahexaenoic acid (DHA) for the treatment of pediatric sport-related concussion: results of a feasibility trial. Orthop J Sports Med.(2019) 29:165. 10.1177/2325967119S00004

Mills JD, Hadley K, Bailes JE. Dietary supplementation with the omega-3 fatty acid docosahexaenoic acid in traumatic brain injury. Neurosurgery. 2011 Feb;68(2):474-81; discussion 481. doi: 10.1227/NEU.0b013e3181ff692b. PMID: 21135750.

Mira RG, Lira M, Cerpa W. Traumatic Brain Injury: Mechanisms of Glial Response. Front Physiol. 2021 Oct 22;12:740939. doi: 10.3389/fphys.2021.740939. PMID: 34744783; PMCID: PMC8569708.

Morris DR, Levenson CW. Zinc in traumatic brain injury: from neuroprotection to neurotoxicity. Curr Opin Clin Nutr Metab Care. 2013 Nov;16(6):708-11. doi: 10.1097/MCO.0b013e328364f39c. PMID: 23945221.

Nakagawa A., Manley G. T., Gean A. D., Ohtani K., Armonda R., Tsukamoto A., et al. (2011). Mechanisms of primary blast-induced traumatic brain injury: insights from shock-wave research. J. Neurotrauma. 28 1101–1119. 10.1089/neu.2010.1442

Nayak R, Attry S, Ghosh SN. Serum Magnesium as a Marker of Neurological Outcome in Severe Traumatic Brain Injury Patients. Asian J Neurosurg. 2018 Jul-Sep;13(3):685-688. doi: 10.4103/ajns.AJNS_232_16. PMID: 30283527; PMCID: PMC6159066.

Neves M Jr, Gualano B, Roschel H, Lima FR, Lu cia de Sa -Pinto A, Seguro AC, Shimizu MH, Sapienza MT, Fuller R, Lancha AH Jr, Bonfa E (2011) Effect of Creatine

Supplementation on measured glomerular filtration rate in postmenopausal women. Appl Physiol Nutr Metab. 36(3):419-22.

Polderman KH, Bloemers FW, Peerdeman SM, Girbes AR. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. Crit Care Med. 2000 Jun;28(6):2022-5. doi: 10.1097/00003246-200006000-00057. PMID: 10890658.

Poortmans JR, Auquier H, Renaut V, Durussel A, Saugy M, Brisson GR (1997) Effect of short-term creatine supplementation on renal responses in men. Eur J Appl Physiol Occup Physiol 76(6):566–567

Poortmans JR, Francaux M (1999) Long-term oral creatine supplementation does not impair renal function in healthy athletes. Med Sci Sports Exerc 31(8):1108–1110

Poortmans JR, Kumps A, Duez P, Fofonka A, Carpentier A, Francaux M (2005) Effect of oral creatine supplementation on urinary methylamine, formaldehyde, and formate. Med Sci Sports Exerc 37(10):1717–1720

Poortmans, J. R., & Francaux, M. (2000). Adverse Effects of Creatine Supplementation. Sports Medicine, 30(3), 155–170.doi:10.2165/00007256-200030030-00002

Prokopidis K, Giannos P, Triantafyllidis KK, Kechagias KS, Forbes SC, Candow DG. Effects of creatine supplementation on memory in healthy individuals: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2023 Mar 10;81(4):416-427. doi: 10.1093/nutrit/nuac064. PMID: 35984306; PMCID: PMC9999677.

Pu H, Guo Y, Zhang W, Huang L, Wang G, Liou AK, Zhang J, Zhang P, Leak RK, Wang Y, Chen J, Gao Y. Omega-3 polyunsaturated fatty acid supplementation improves neurologic recovery and attenuates white matter injury after experimental traumatic brain injury. J Cereb Blood Flow Metab. 2013 Sep;33(9):1474-84. doi: 10.1038/jcbfm.2013.108. Epub 2013 Jun 26. PMID: 23801244; PMCID: PMC3764381.

Sakellaris G, Kotsiou M, Tamiolaki M, Kalostos G, Tsapaki E, Spanaki M, Spilioti M, Charissis G, Evangeliou A. Prevention of complications related to traumatic brain injury in children and adolescents with creatine administration: an open label randomized pilot study. J Trauma. 2006 Aug;61(2):322-9. doi: 10.1097/01.ta.0000230269.46108.d5. PMID: 16917445.

Sakellaris G, Nasis G, Kotsiou M, Tamiolaki M, Charissis G, Evangeliou A. Prevention of traumatic headache, dizziness and fatigue with creatine administration. A pilot study.

Acta Paediatr. 2008 Jan;97(1):31-4. doi: 10.1111/j.1651-2227.2007.00529.x. Epub 2007 Dec 3. PMID: 18053002; PMCID: PMC2583396.

Saraiva AL, Ferreira AP, Silva LF, Hoffmann MS, Dutra FD, Furian AF, Oliveira MS, Fighera MR, Royes LF. Creatine reduces oxidative stress markers but does not protect against seizure susceptibility after severe traumatic brain injury. Brain Res Bull. 2012 Feb 10;87(2-3):180-6. doi: 10.1016/j.brainresbull.2011.10.010. Epub 2011 Oct 25. PMID: 22051612.

Scheff SW, Dhillon HS. Creatine-enhanced diet alters levels of lactate and free fatty acids after experimental brain injury. Neurochem Res. 2004 Feb;29(2):469-79. doi: 10.1023/b:nere.0000013753.22615.59. PMID: 15002746.

Schubert R, Kitz R, Beermann C, Rose MA, Lieb A, Sommerer PC, Moskovits J, Alberternst H, Böhles HJ, Schulze J, Zielen S. Effect of n-3 polyunsaturated fatty acids in asthma after low-dose allergen challenge. Int Arch Allergy Immunol. 2009;148(4):321-9. doi: 10.1159/000170386. Epub 2008 Nov 11. PMID: 19001792.

Slankamenac J, Ranisavljev M, Todorovic N, Ostojic J, Stajer V, Candow DG, Ratgeber L, Betlehem J, Acs P, Ostojic SM. Eight-Week Creatine-Glucose Supplementation Alleviates Clinical Features of Long COVID. J Nutr Sci Vitaminol (Tokyo). 2024;70(2):174-178. doi: 10.3177/jnsv.70.174. PMID: 38684388.

Slankamenac J, Ranisavljev M, Todorovic N, Ostojic J, Stajer V, Ostojic SM. Effects of six-month creatine supplementation on patient- and clinician-reported outcomes, and tissue creatine levels in patients with post-COVID-19 fatigue syndrome. Food Sci Nutr. 2023 Sep 20;11(11):6899-6906. doi: 10.1002/fsn3.3597. PMID: 37970399; PMCID: PMC10630839.

Smith GI, Julliand S, Reeds DN, Sinacore DR, Klein S, Mittendorfer B. Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. Am J Clin Nutr. 2015 Jul;102(1):115-22. doi: 10.3945/ajcn.114.105833. Epub 2015 May 20. PMID: 25994567; PMCID: PMC4480667.

Sullivan, P. G., Geiger, J. D., Mattson, M. P., & Scheff, S. W. (2000). Dietary supplement creatine protects against traumatic brain injury. Annals of Neurology, 48(5), 723–729.doi:10.1002/1531-8249(200011)48:5<723::aid-ana5>3.0.co;2-w

Tagliaferri, F., Compagnone, C., Korsic, M., Servadei, F., & Kraus, J. (2005). A systematic review of brain injury epidemiology in Europe. Acta Neurochirurgica, 148(3), 255–268.doi:10.1007/s00701-005-0651-y

Temkin NR, Anderson GD, Winn HR, Ellenbogen RG, Britz GW, Schuster J, Lucas T, Newell DW, Mansfield PN, Machamer JE, Barber J, Dikmen SS. Magnesium sulfate for neuroprotection after traumatic brain injury: a randomised controlled trial. Lancet Neurol. 2007 Jan;6(1):29-38. doi: 10.1016/S1474-4422(06)70630-5. PMID: 17166799.

Tsuchiya Y., Yanagimoto K., Nakazato K., Hayamizu K., Ochi E. Eicosapentaenoic and docosahexaenoic acids-rich fish oil supplementation attenuates strength loss and limited joint range of motion after eccentric contractions: A randomized, double-blind, placebo-controlled, parallel-group trial. Eur. J. Appl. Physiol. 2016;116:1179–1188. doi: 10.1007/s00421-016-3373-3.

Wang R, He M, Xu J. Initial Serum Magnesium Level Is Associated with Mortality Risk in Traumatic Brain Injury Patients. Nutrients. 2022 Oct 7;14(19):4174. doi: 10.3390/nu14194174. PMID: 36235826; PMCID: PMC9570645.

Wang T, Van KC, Gavitt BJ, Grayson JK, Lu YC, Lyeth BG, Pichakron KO. Effect of fish oil supplementation in a rat model of multiple mild traumatic brain injuries. Restor Neurol Neurosci. 2013;31(5):647-59. doi: 10.3233/RNN-130316. PMID: 23835930.

Wilson L, Stewart W, Dams-O'Connor K, Diaz-Arrastia R, Horton L, Menon DK, Polinder S. The chronic and evolving neurological consequences of traumatic brain injury. Lancet Neurol. 2017 Oct;16(10):813-825. doi: 10.1016/S1474-4422(17)30279-X. Epub 2017 Sep 12. PMID: 28920887; PMCID: PMC9336016.

Wu A, Ying Z, Gomez-Pinilla F. Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. J Neurotrauma. 2004 Oct;21(10):1457-67. doi: 10.1089/neu.2004.21.1457. PMID: 15672635.

Young B, Ott L, Kasarskis E, Rapp R, Moles K, Dempsey RJ, Tibbs PA, Kryscio R, McClain C. Zinc supplementation is associated with improved neurologic recovery rate and visceral protein levels of patients with severe closed head injury. J Neurotrauma. 1996 Jan;13(1):25-34. doi: 10.1089/neu.1996.13.25. PMID: 8714860.

Young L. A., Rule G. T., Bocchieri R. T., Burns J. M. (2015). Biophysical mechanisms of traumatic brain injuries. Semin. Neurol. 35 5–11. 10.1055/s-0035-1544242