The possible role of hydration in concussions and long-term symptoms of concussion for athletes. A review of the evidence

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Abstract
The purpose of this review is to address what is known, speculated, and hypothesized regarding the issue of hydration and concussions. Based on the question, “What impact does hydration have on the relative risk for suffering concussive injuries along with long-term ramifications that have been associated with concussive (and repeated subconcussive) traumas to the cerebral cortex?,” a search of available literature was performed through June 2019. Deducing from the available literature, we can stipulate that changes in hydration within the cerebral cortex increase the likelihood for disruption of neurofilament proteins, dysregulation of membrane dynamics of the neurons and exacerbate inflammation responses following head trauma. As such, it can be speculated that differences in incidence rates may be attributed to difference in tissue fluid based on athlete demographics, level of whole-body water balance, and degree of tissue dehydration more than selection of sport. Moreover, tissue hydration in combination with other inflammation factors provides the scaffolding for the development of long-term issues (e.g. chronic traumatic encephalopathy) associated with repetitive head trauma in athletes.

Keywords
Concussion, hydration, post-concussion syndrome, chronic traumatic encephalopathy

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Introduction
We have come to associate concussions with sports. Yet, sports-related concussions account for only 15.5% of all concussions. Of this athletic population, the greatest incidence of concussion appears to be in boxing and mixed-martial arts, followed by football and then hockey, soccer, and lacrosse.1–4 Additionally, there appears to be a greater rate of concussions occurring in female athletes relative to their matched male counterparts.5–7 Concerns around concussion and head injuries in athletes have not been a recent phenomenon (even with the increased media attention) with decades of progressive attempts to develop better protections to the head and cerebral cortex of athletes that compete in high impact and contact sports (e.g. American Football, Ice hockey, Rugby, Boxing, and Martial Arts).6,8–14 Leading to a concerted effort to develop better equipment and practices to prevent concussions from developing in the first place or protocols to immediately treat any head injury after a potential concussive event.1–3,9,11,15–18 Most of these efforts have been focused on: (1) developing better protective equipment, (2) limiting potential head contacts, (3) immediate diagnosis and treatment to any head contact, and (4) recognized treatment protocols and time course for return to play following head trauma.1,3,11,15 Unfortunately, most equipment developed are better at reducing the linear forces imparted on the head than the angular accelerations that can cause injuries beyond the coup and counter-coup
injury (Figure 1). All of which has led to findings that show minimal reduction in the total incidence of concussions in across sports. Since prevention plans have not impacted rates of concussion, it implies that secondary issues may be at play that go beyond the biomechanics of the impact involved in the formation of a concussion. A speculation supported by reports (both anecdotally and empirically) of long-term cognitive issues in former athletes either have no reported concussive injury or whose sport of choice has a very low incidence rate for concussion injuries for athletes. These later reports along with the physiological responses (e.g. episodes of hypohydration or acute dehydration) associated with sports led to a hypothesis in 2014. A hypothesis that indicated dehydration leads to reduction of cerebrospinal fluid (CSF) that may be the underlying culprit in the incident of a concussion in athletes. A postulate which makes sense given that one of the commonly accepted roles of CSF is dampening impact forces placed on the cerebral cortex (Table 1) or impact the integrity of neurofilamentous structures within the neurons. Previous research has indicated that a threshold of impact force of 50–100 g on the cerebral cortex is typically associated with development of a concussion or concussion-like symptoms. Yet, most head trauma that athletes undergo during the course of competition falls below this threshold (approximately 20 g) can still result in cellular trauma that is comparable to damage following a concussive injury.

Unfortunately, limited investigation into this hypothesis indicated no difference in the incidence of concussion rate between conditions that should induce dehydration, i.e. high temperature environments versus ideal environmental condition. Yet, it must be indicated that this line of investigation focused more on environmental factors that would induce greater levels of dehydration and not dehydration itself. Additionally, these investigations fail to examine if lack of differences comes from effort of the athletic trainers and sports medical staff to ensure proper hydration during exertion in these less than favorable environmental conditions may not offset changes of hydration that can impact neural hydration or CSF properties and functions. Furthermore, the investigations neglected to examine any impact of hydration based on body composition (i.e. fat mass). Where those with greater total fat mass (e.g. female or overfat athletes) have a lower total water content and thus may have a greater likelihood to have cellular and tissue dysregulation-based hydration issues. As such, flaws in methodology may limit our understanding of concussions within sports as physiological and anatomical differences in distinct populations (i.e. females and overfat athletes) were not taken into account within the analysis. Therefore, if we examine conclusions drawn from the aforementioned postulate in combination with the speculated relationship between hydration in the development of Alzheimer and Alzheimer’s like dementia, a more pertinent question arises. What impact does hydration have on the relative risk for suffering concussive injuries along with long-term ramifications that have been associated with concussive (and repeated sub concussive) traumas to the cerebral cortex?

Hence, the purpose of the review is to address what is known, speculated, and hypothesized regarding this issue. In which we will attempt to address three key aspects related to the issue of concussions and long-
Table 1. Events and the impact forces encountered by athletes associated with risk for concussion or sub Concussive injuries.2,10,14,25,35,37,47

| Sport – Event in Sport/Movement | Indicated g-force (g) | Indicated angular acceleration (rad/sec²) |
|-------------------------------|----------------------|----------------------------------------|
| Soccer – Head-to-Object (Ball) | 12–55                | 750–3000                                |
| Soccer – Head-to-Head          | 87                   | 7033                                    |
| Hockey – Head-to-Object/Head-to-Person (Female) | 31–55                | 2600–5470                               |
| Hockey – Head-to-Object/Head-to-Person (Male) | 50–100               | 5000                                    |
| Youth Hockey                  | 18–46                | 1400–4150                               |
| American Football – Head-to-Person/Head-to-Head | 19–100               | 930–5000                                |
| Youth American Football – Head-to-Person/Head-to-Head | 16–21               | 690–1410                                |
| Baseball – Head-to-Object (Ball and Helmet/Mask) | 26–42                | 1974–5266                               |

*Position dependent with defensive linemen greater total impacts with higher angular acceleration; running backs, receivers, and defensive backs greatest angular acceleration; quarter backs greatest linear accelerations.

From the returns of each independent search, a total of 10,837 returns were screened by title and abstract, with 277 articles previewed, leading to a review of 65 of articles related to the primary question. Interestingly, given the speculation of dehydration on the incidence of concussion and the relationship between concussion and chronic traumatic encephalopathy (CTE), the combinations of key terms in any order (dehydration and concussion or hypohydration and concussion, or with chronic traumatic encephalopathy) continually returned 0 abstracts and articles for screening from the searchable databases.

In addition to the 65 articles returned in our search, 12 articles were included from a previous review of the literature by the authors on this topic and from references provided by articles reviewed. The finalization of the hypothesis presented involved the inclusion of additional review of underlying factors associated with hydration status. To address the underlying factors, four additional articles related to nutrition, thermoregulation, body size, and morphology on hydration were also included following the initial review that allowed for the formation of overall hypothesis.

Potential role of hydration in concussions and long-term issues

Mechanisms of concussion and understanding risk

The cerebral cortex must be able to withstand a diffuse impulse force wave that radiates from the region of impact through the entirety of the cerebral cortical tissues and not just at the points of contact (Figure 1).17,18,20,27,28,35,38,43–45 As O’Connor14 points out that there is a proposed mechanical threshold for impact that indicates a tolerance for concussive injury being up to 96 g of linear acceleration and 5582 rads/s² of angular acceleration. Yet, the same author points...
that even with these limits, angular accelerations as low as 2911 rads/s² or linear acceleration of 31.8 g may provide enough stimulus to induce concussion symptoms. Yet, the severity of the symptoms and functional losses that indicate the amount of force being placed across the axons indicates the damage of the tissue that extends beyond these areas of contact. The pressure waves generated by the impact will drives through the interstitial fluids (i.e. CSF) via inertial movements and forces, disrupting the cortical tissues and leaves neurons susceptible to injury. Susceptibility that is impacted by factors that alter the ability for cortical tissues to withstand these pressure waves (i.e. hydration, inflammation responses), where impacts that would otherwise be withstood lead to injury.

An important factor to understand is that various athletic movements will place acceleration forces on the cerebral cortex as low as 20g may induce diffuse axon injuries similar to what is seen with concussion injuries. While the degree of impulse from a single contact may not be sufficient for inducing noticeable symptoms of a concussion (i.e. subconcussive trauma), the repeated impact of these subconcussive traumas is progressive and in totality can instigate concussive symptoms for the athletes.

An issue that is especially important for athletes when recovery periods are not sufficient enough to allow full resolution of injury. There are also change in the forces and accelerations imparted onto the cerebral cortex based on age and level of mastery for the athlete that is in disagreement to what one might expect. The younger and the less experienced athlete appear to be subjected to greater forces than those experienced by older and more experienced athlete. Additionally, there are the gender and body compositional differences that can impact the physiological responses impacting the ability to resist impact forces based on the hydration of the athlete, which directly alters the severity of symptoms that arise following trauma. Issues that are compounded as the generally agreed upon increased relative risk of suffering a concussive injury as training methods and nutrition have allowed for larger and faster athletes to compete across all sports.

**Potential impact of hydration in concussion and symptoms**

Given the multitude of mechanism at play in the development of concussion and concussion symptoms and the inability to effectively prevent concussions in totality, we must explore a common factor impacting all athletes, the ability to stay hydrated. Changes in hydration impact cerebral function in two principal ways: first, hydration will alter the protective structures of the cerebral cortex (e.g. CSF, meninges); second, hydration will impact the cellular structures of the neuron (i.e. neurofilament integrity and axolemma) and membrane dynamics leading to changes in neuronal functions. Extrapolating from these points, one can stipulate that hydration impacts both protective structures and the level of inflammation following head trauma (Figure 2). The changes in hydration limit the ability of the tissues to withstand the pressure wave of impact that will pass through the cerebral cortex (Figure 1).

As indicated earlier, mechanisms underlying prevention of concussion are based on the ability of the cerebral cortex to withstand single and repetitive acceleration changes due to rapid movements of the head associated with sports. Anatomically, there are two key features (the connective tissues of cerebral cortex and CSF) that serve as a means of dampening g-forces and protect the fragile cerebral cortex from excessive g-force due to rapid movements of the head and impact moments during contact associated with sports. Principally, this will be done by the CSF. Where the assumption is that density of CSF (998 kg/m³) acts as medium to keep the cerebrum buoyant within the cranial vault while at the same time the viscosity (1.003 g/m s) functions in such a way as to reduce the impulse moments during rapid acceleration and deceleration moments associated with sports.

Any change in hydration status directly changes the available volume of CSF produced – changes that alter both the chemical composition and physical properties of CSF that alters kinematics of the connective tissues that surrounds the cerebral cortex. Alterations of CSF are due to changes in diffusion coefficient, blood flow, and both fluid pressures and volumes. That will impact the circulation of CSF. Normally, CSF circulates throughout the central nervous system, from the choroid plexus through the cortex into the meninges and then along the spinal cord and then back the cerebral sinuses – a flow that ensures that meningeal layers are not in direct contact with each other while also providing the support to keep the cerebral cortex, spinal cord, and supporting tissues and structures from becoming trapped within the bony architecture of the enveloping bones. However, as dehydration induces changes in CSF, the flow is impacted resulting in changes within the anatomy and kinematics of the meninges and the overall buoyancy that allows for the central nervous system to float within the bones. In particular, the arachnoid layer (where the majority of CSF circulation takes place) will be greatly affected and result in a reduced space between pia and dura mater. Additional changes would be expected within the subdural spaces, folds, and ventricles of the meninges, changes that allow us to stipulate that the reduction of fluid moving through the
meninges disrupts the protective barrier between the bony architecture of the cranial bones and the cerebral cortex. What’s more, this change may cause binding between the pia and dura mater layers and increases the lines of tension within and surrounding the cerebral cortex. When combined with other anatomical and physiological modifications resulting from dehydration, and fluid shifts during sports, explain how changes in hydration alter the relative risk for experiencing concussions or damage from repetitive subconcussive trauma in athletes, thereby indicating that dehydration increases the relative risk for experiencing a concussion either from a single threshold event or repetitive subconcussive events (either a single athletic event or multiple athletic events) should recovery not be sufficient.

Body compositional impact on hydration and influence on concussion

These changes may be amplified when body compositional issues (i.e. increased fat mass) are taken into account. An increased fat mass directly reduces total body water and volume that can be lost prior to onset of dehydration-related fluid shifts, a factor that may underlie differences seen in some athletes being at greater risks for suffering issues related to concussion (or repetitive subconcussive) trauma. As there has been some research into differences in incidence and prevalence based on gender, yet no such research to date has looked specifically at the incidence rates in regard to differences based on the body composition of the athlete. We can extrapolate from here to indicate that morphological differences (i.e. fat mass) between males and females provide a perspective that total body water is a reason for a greater relative risk for dehydration and fluid shifts and the resulting increased risk for concussion for the female athlete. It would follow a similar logical process to extrapolate this difference in morphology and fat mass to explain possible differences in concussion rates and long-term ramifications that may be seen between normal fat and overfat athletes. Those who have less water mass at the start of play, or are more prone to lose excessive fluids during play, can experience larger changes of intratissue fluid volumes resulting in greater changes in the CSF production rate, thereby resulting in a larger shift in the chemical and physical properties of the fluid that is ultimately produced and eliciting greater loss in the protective tissues and fluids surrounding the cerebral cortex. Secondarily, it must be indicated that larger and/or overfat athlete tend to have poor thermoregulators. Thus, larger athletes will have greater sweat rates than those athletes that are smaller or with less fat. A phenomenon

Figure 2. The combination of factors stemming from the change in hydration leading to reduction in ability to withstand axonal shearing culminating in the inflammatory responses allowing for tau and amyloid protein accretion and cellular dysregulation and functional losses associated with concussion injuries. Note that indicates downstream impact, that indicates stemming from reduced hydration, that indicates stemming from reduced volumes of fluids (TBV or CSF), that indicates stemming from tissue dehydration, and that indicates stemming from decreased Neurofilament elasticity and from increased diffuse axonal injuries.
combined with a greater fat mass and a possibly reduced water content, as with the female athlete, leads the large and/or overweight athlete to possibly experience larger changes in fluid volumes. If one were to combine these postulates, a rationale for the changes in incidence rate of concussions reported for sports like American Football becomes evident. This rationale may be even more evident should one take into account the exposure to environmental conditions that lead to greater risks for large fluid shifts to attempt to thermoregulate appropriately, as seen in American Football. Issues at play even when evaluation for dehydration place them below the cusp of indicating dehydration. Moreover, the overweight athlete may also have a greater risk for concussions due to inflammatory signals that modify metabolism leading to compensatory responses that subsequently impact not only the available fluid within the body to thermoregulate appropriately (i.e. sweat) but also still ensure proper tissue fluids. The resultant impact on normal intratissue and intertissue fluid shifts necessary to ensure normal chemical/physical properties of the fluids of the body may also subsequently hinder normal recovery mechanisms when combined with chronically elevated inflammatory signals. An issue that is not normally thought about in regard to high-level athletes, yet is a prominent issue given the epidemic rise of overweightness in the population and the public health initiative to have overweight adolescents actively engage in athletic events, including those where head trauma has a high likelihood (e.g. American Football, Rugby, and Ice Hockey).

**Hydration and changes in CSF and meninges**

Changes of CSF directly alter the functions of the tissues serving as a layer of protection to the cerebral cortex and the neurons themselves, reducing the tissues ability to resist shear and torsional force occurring during any head impact and the resultant transmission of energy throughout the cerebral tissues, causing diffuse axonal injuries. There are several reasons that changes in hydration directly changes the ability for the cerebral cortex to withstand impact forces from either a single concussive episode or repetitive sub concussive episodes sustained during athletic play. One of which is the anatomical modification that takes place within the ventricles. While generally indicated as being small in anatomical size relative to the axonal and cortical tissues that surrounds them, the ventricles provide a great benefit to the cerebral cortex. The open space within the ventricles (containing non-compressive CSF) should act as a damper to the transmission of energy waves through the cerebral cortex (Figure 1) associated with head injury. Any reduction in formation of CSF will lead to a reduction in both the compressibility and, possibly, the overall volume, of the ventricles. The hydration shifts that impact the functional anatomy of the ventricle increase the relative risk for cortical and axonal damage from rapid accelerations or decelerations of the head. Changes that are most likely the results of changes in the mechanisms regulating CSF production (e.g. diffusion coefficient changes, reduced blood flow and volume, alteration of osmotic differences between the cells of the choroid plexus and the surrounding fluids) that will alter the fluid volume within the ventricles. The impact within the ventricle seems paradoxical. As mild levels of dehydration will induce a reduced ventricular volume, increasing severity of dehydration causes ventricle volume to actually increase. Changes that may alter connections between the various connective tissue layers, impacting cortical function as the reduction of ventricle volume may increase axonal tension while enlargement may occur in conjunction with compaction of the cortical gray matter. Yet, Watson et al. have indicated that mild exercise-induced dehydration appeared to little impact on ventricle characteristics and volumes even with fluxes in cerebral perfusion, stability of the choroid plexus capillary network, and overall intracranial pressures following head injuries impacting CSF. However, even these small (insignificant) changes may in actuality produce conditions that rise the risk for injury to the cortical tissues and thus concussion for the athlete. Given that any change in volume will directly alter the lines of tension along the axonal projections and thereby place the tissues at greater risk for exceeding its yield point (i.e. maximal tension or compression) and thus allow for injury to be reached at lower magnitudes of g-force.

As with any fluid movement, the production of CSF will be impacted and governed by Starling's law for fluid movements along with hormone regulation of the permeability at the choroid plexus. Thereby, one can assume that the volume of CSF being produced is regulated by hormonal osmolarity regulation (i.e. antidiuretic hormone, aldosterone, angiotensin II), cation concentration (i.e. Na⁺, Ca²⁺), and the anion gap (i.e. concentrations of Cl⁻, HCO₃⁻) between the CSF, choroid plexus, and plasma. While a majority of the changes in production is directed by the change in hydration, other factors also impact CSF production for athletes. A secondary change in CSF will occur due to increased physical activity independent of total hydration. An increase in physical activity leads to a change in the anion gap, namely a reduction in the anion gap (a plasma shift toward acidotic state) altering rate of CSF production and may lead to intratissue hydration fluctuations and complications for neurons
and their associated glial cells. Thus, we can speculate that even without noticeable shifts in total hydration status (i.e. urine specific gravity (USG) indicating euhydration), there may be deleterious shifts of fluid taking place around the neurons of the cerebral cortex to compensate for changes in anion gaps and plasma chemistry.

Changes in CSF production will alter the chemical composition of the fluid. Compositional changes have deleterious effects on the integrity of the axolemma and the structural integrity of the neurofilaments and microtubules, impacts which may occur independent of the amplitude of trauma to the cerebral cortex.15,17,27,33,38,43,46,60,61 Alteration in CSF composition directly impacts its function as an interstitial fluid to allow for proper ion balance, thus, altering membrane kinematics of the neurons within the cerebral cortex. As such, dehydration may allow for cellular damage to take place independent of the degree of trauma (i.e. head injury).17,38,43,60,61 Additionally, alteration in neuron function from dehydration may make it difficult to properly evaluate and diagnose a concussion in the dehydrated athlete.62 If we were to extrapolate from this postulate, it can be assumed that the two issues (i.e. tissue fluid changes and head trauma) run parallel to and may compound on each other. A resultant effect that may explain why there was no indication for changes in concussion incidences during play under conditions that should cause excessive dehydration.2,39 Where, it was noted that the sports medical staff attempted to maintain hydration, indicated by USG being lower than the designated level of dehydration (i.e. USG ≥1.025). Yet changes and shifts in fluid chemistry may place players at risk for concussions even if they remained below that threshold for being labeled dehydrated. Meaning that even while attempting to keep athletes hydrated, the threshold for ensuring whole-body hydration (i.e. USG <1.025) may not provide a buffer necessary for maintaining normal CSF chemical and physical properties. Unfortunately, this postulate cannot be ascertained without independently assaying changes in plasma and body fluid chemistry that results from fluid shifts occurring during active periods of play. Furthermore, play-to-play shifts in tissue hydration may not be negated by periods of rest and rehydration within the single athletic events (either practice or competition). A postulate that has limited evidence to date, but deserves much more research than has been allotted, yet ethical concerns may limit the ability to perform said research.

Additionally, concussive forces may also have an impact on the anatomy of the blood-brain barrier based on alteration in perfusion rates and pressures and then the total change to intracranial pressures is generally assumed to occur following head injuries.36,50,51 These changes can be observed for weeks and months after concussion injuries and is linked with alteration of blood flow, fluid shifts, and inflammation markers following concussive injuries.24,36,50–52 Alterations that may impact CSF production along with chemical composition of the CSF surrounding the neurons and flow from the choroid plexus to the cerebral sinuses within the meninges. Any changes that impede acute resolution may lead to less than favorable outcome,50,52 yet limited evidence to the directional effect limits our ability to conclude one way or another on the either short-term or long-term impact and once again more investigation is warranted.

Hydration, concussion, and the responses at the neurons

Regardless of the total amplitude of changes in volumes of fluid within the body stemming from exertional-induced dehydration, the impact of concussive forces will inevitably filter onto the neuron itself.17,33,38,59–61 The forces experienced at the axons and along the axonal tension lines may not be from the direct motion of, or in line with, the movement of the head impact (Figure 1) and result in the diffuse axonal injuries that are a hallmark sign of concussive injury.27,45 The diffuse axonal injury can be seen as linked to the level of hydration within the tissue, if not whole-body hydration altogether.26,33,40,43,63

Axonal injuries that occur across the axolemma results in dysregulation of protein channels resulting in uncontrolled ion (i.e. Na⁺, K⁺, Ca²⁺) flux and neurotransmitter (e.g. glutamate) effects throughout the region of injury.17,26,33,36,59,63 Moreover, the fluxes in CSF composition from changes in hydration exacerbate the ion fluxes seen following the diffuse axonal injury. Fluxes in ion movement and glutamate dysregulation are exacerbated by the resultant swelling throughout the axons that triggers additional dysregulation within the axolemma.33,36,46,63 Dysregulation may be increased in those individuals who are genetically predisposed to having inflammatory and swelling issues following head injuries.33,63 Or in those that are being exposed to rapidly repeated pressure waves that are traversing through the cerebral cortex inducing greater dehydration within the tissue. Moreover, dehydration of the tissues changes the structure of neurofilaments of the axon leading to the formation of filamentous tangles.15,26,33,38,43 Formations which can occur independent of the absolute impact forces experienced. These tangles can lead to the formation of tau and amyloid protein plaques within and around terminal branches of axons and dendrites of the neurons commonly linked with neurodegenerative diseases (e.g.
CTE, amyotrophic lateral sclerosis, Alzheimer’s disease.26,33,36,38,43,64 Yet, as with previously stipulated speculation, there is limited evidence to draw a conclusive theory to explain the phenomenon, and more research is warranted. What’s more, one can speculate that tissue hydration impacts the neurofilaments. The shifts of fluid within the cell and tissues can lead to alteration in the tertiary and quaternary proteins structures, thus reducing the functionality of the proteins. A similar phenomenon is seen in causing the failure of other tissues (i.e. tendon and ligament). In which repeated stress across the tissues induce changes to hydration that changes the ability to withstand continuous tension and torsional forces, thus resulting in orthopedic injury, thereby leading to the crux of an argument regarding the relationship of hydration and concussion. Thus those who are more susceptible to chronic fluid fluxes within the tissues of the cerebral cortex may experience greater overall damage. An idea that is founded on the concept that when the tissue itself becomes excessively dehydrated, it will not be able to withstand the forces imparted from torsional and shear impact forces during athletic impacts to the head. Thus, increasing the relative risk for additional diffuse axonal injury and resulting in greater chances for dysregulation. Dysregulation that increases likelihood of injury to the neuron is a process very similar to the dysfunctions of associated with repetitive trauma to similar protein structures seen in tendons and ligaments of the musculoskeletal system. Ergo, we can speculate that there is an interplay between tissue hydration and diffuse axonal injuries based on gender and overfatness. Individuals within either population have distinct disadvantages as it relates to hydration by body mass and higher than normal levels of inflammation (especially in the overfat population).7,41,57 Both factors (dehydration and chronic inflammation) are involved with the onset of dysregulation and degeneration in other tissues that are regularly injured by athletes.

From this perspective, we can argue that cytoskeletal disruption stemming from dehydration of neurotubules and neurofilaments may have a greater total impact on severity of injury and long-term impacts than the actual mechanism causing diffuse axonal injuries. This disruption of cytoskeletal function makes axons and surrounding connective tissue unable to withstand shearing forces (angular acceleration derived) or the point of impact (linear impact) forces.26,27,38,44,45 Instability that places the neuron at an increased risk for additional damage would trigger further filamentous stress and tangle formations.38,43,60,64 Along with triggering intracellular swelling dysregulation and instability of the axolemma impacts, the ability for the neuron to initiate repair can possibly lead to phosphorylation of the frayed filaments causing the tau and amyloid accumulations within and surrounding the focal points of the injury.33,36,38,43,60,61,63–65 A process that itself triggers additional dysregulation outside the immediate loci of injury and results in an instigation of a glial-mediated inflammatory responses, that if left unresolved lead to long-term issues for the athletes following a concussive injury or repetitive subconcussive injuries.

### Inflammation, hydration, and concussions

In addition to the dysregulation initiated by changes in hydration, trauma will induce an inflammatory response based on glial (astrocytes and microglia) cells release of a host of inflammatory biomarkers

| Inflammatory signals | Growth signals | Dehydration signals | Genetic Markers |
|----------------------|----------------|---------------------|-----------------|
| NSE                  | Brain-derived neurotrophic factor (BDNF) | S100β | Apolipoprotein |
| S100β                | cortisol       | Tau                | GFAP            |
| GFAP                 | Creatine kinase| Cortisol           | Tau             |
| Creatine kinase      | Cortisol       | Tau                | GFAP            |
| Cortisol             | Tau (P-tau and T-tau, cleaved tau) | Apolipoprotein | Tau             |
| β-Amyloid            | Fatty-acid binding protein | Tau | GFAP |
| NFL                  | Alpha-II spectrin | Apolipoprotein | Tau |
| TDP                  | Myelin basic protein | Apolipoprotein | Tau |

Table 2. Biochemical signals and genes associated with growth, inflammation, and dehydration that may impact neuron anatomy and physiology following concussive or repetitive sub concussive injuries.12,36,63
Biomarker activity subsequently exacerbates the impact that changes in fluid dynamics have on the ability to resolve any axonal injuries. The most common of these markers is S100β and is seen elevated in athletes during periods of exertional induced dehydration independent of any level of head injury. These inflammatory responses to head trauma are thus compounded by the effect of hydration changes associated with play and will directly impact the ability for the athlete to recover from any degree of head injury suffered during a period of exertion. Deleterious results are due to both factors linked to the formation of tangles within the axons and protein plaques surrounding the neurons along with protein disruption known to induce neurodegenerative issues later in life. More importantly, these compounding issues may be problematic for younger athletes due to inflammation initiating the cascade of events linked with neurological degeneration (Figures 2 and 3), occurring within a period necessary for normal neuronal growth and the extensive plasticity required for maturation of the cerebral cortex. Effects which may explain why head trauma during childhood and adolescence can lead to long-term ramifications (e.g. CTE) for those that continue participations in sports with higher levels of known head contacts.

The degree of change in the inflammatory biomarkers (i.e. tau, S100β, neurofilament light protein (NFL), glial fibrillary acidic protein (GFAP)) correlates with the severity and duration of concussion without any indication to the severity of the outcome of the concussion. Changes that can be seen without diagnosis of concussion may last up to two weeks post event for combat athletes (e.g. boxers) with certain markers (i.e. S100β, neuron-specific enolase (NSE)) remaining elevated for months after the traumatic event. Accompanying these intracellular and inflammatory changes is a shift in total perfusion and generation of CSF circulation through the tissues. From which one can speculate that the change in CSF flow and increased inflammation accompanying tissue dehydration creates a favorable environment for tau and amyloid accretion, even without diagnosed concussion for the athlete. This combination of inflammatory biomarkers following shear and torsional axonal injury with fluid shifts associated with exertion may provide a foundation for the sequelae of events leading to long-term issues from repetitive subconcussive traumas. Further it provides a rationale for why issues arise more often in those more susceptible to fluid shifts and dehydration during athletic events prior to experiencing any stresses to the axons from head impacts. The combination of trauma and dehydration explains how symptoms stemming from a concussive impact arise from areas outside of the region (i.e. coup and countercoup) of impact. Additionally, the impact of hydration provides insight into why some symptoms may be seen more chronically than acutely for those suffering a concussive injury. The resulting combination of inflammation and dehydration accentuates the formation of tau protein entanglements and amyloid plaques that disrupt normal neuronal functions.

Figure 3. Cascade of events from the original injury to the neuronal death, tissue loss, and functional deficits that is based on the accumulating amounts of inflammation and neurofilaments tangles at the synapse that leads to develop of symptoms associated with CTE.
sequence forms the foundation within the sequelae of events of dehydration and head impact leading to tau or amyloid plaque formations and ultimately the long-term issues surrounding both repetitive concussive and subconcussive injuries. Thus, we can stipulate a general hypothesis that the combined dehydration accompanying trauma and the subsequent inflammation responses provide the scaffolding for why some post-concussive issues take years to develop, independent of the level of impact. Unfortunately, with the sparsity of empirical observations for humans, we cannot go beyond speculation at this point in time, and as with other postulates that have been presented, more research is necessary to fete out any causal effects.

Even so, there is ample evidence to indicate that diffuse axonal injuries lead to neurofilament dysregulation and the release of tau and amyloid proteins from the terminal branches of neurons impacted. Yet the empirical evidence to definitively conclude that any single factor associated with the onset of a concussion is the sole underlying reason for the long-term issues with any confidence is lacking at this time. Especially given the cavalcade of confounding variables that impact human health, even if there is the association between the accretion of tau and amyloid to the neurodegenerative diseases and the relationship between trauma inducing tau formation and poor circulation of CSF associated with accretion of amyloid and tau plaques.

As such, there are a couple of factors that become apparent within the relationship of tissue hydration and concussions or repetitive subconcussive trauma. First, repetitive impacts can lead to dehydration within the tissues due to fluid movement accompanying inertial movements during the impact. Second, there is a general understanding that body composition impacts the level of total body water. As those who have greater fat mass (or at least are larger) are more susceptible to fluid shifts that may impact the acute issues of head trauma, a similar difference is indicated for the female athlete in relation to the male counterpart. Therefore, one can speculate that those with greater fat mass may have increased the susceptibility to dehydration and therein suffering a concussion or issues from repetitive sub concussive injuries. Third, dehydration can modify symptoms and alter the ability to effectively and properly diagnose the athlete immediately following trauma, impacting acute treatment and stymie proper long-term care for the injured athlete.

**Long-term implications and the issues of CTE**

There is the foundation for development of long-term ramifications for the athlete suffering head trauma, without regard to the degree of severity, coming from the combined impact of hydration and inflammation. A foundation that serves as the linkage of concussion and the long-term impacts typically revolves around the various symptoms of CTE (Figure 3). A linkage that is related to poor resolution of inflammation that is associated not only with hormonal signals altering inflammation responses but also overall hydration for those that have suffered concussion, or repetitive sub concussive, injuries. In which the injuring event leads to damage and inflammation that remains unresolved, leading to blockage of fluid (i.e. CSF) movement through cerebral cortex. Blockage that in turn leads to neurofilamentous tangles within stagnant fluid that blocks synaptic actions within damaged regions of the cerebral cortex. Thus, the combination of hydration shift with repetitive head injuries, without regard to the severity of injury, increases the likelihood of spongiform disease.

To wit, it can be asserted that no single factor of head trauma can be indicated as the root cause for the onset of degenerative diseases developed from repetitive concussive (or even subconcussive) injuries without examining these underlying responses to fluid shifts and inflammatory biomarkers. Therefore, CTE should be viewed as a syndrome formed as a progressive resultant of the combination of tissue dehydration with accumulated diffuse axonal injuries stemming from repetitive injuries and unresolved inflammation. Where the long-term outcomes of trauma that has been reported may stem from exacerbation of damage originating from repeated bouts of mild impact forces combined with tissue dehydration instead of any single traumatic event.

Yet, we must be careful in the stipulation or confirmation that any athletic head contacts will result in the development of CTE. As there are many variables that contribute to a multifaceted disease like CTE and until we are able to determine the impact of all of the risk factors and time course for onset of symptoms and functional loss, we must all take the position of the ounce of prevention and awareness for immediate treatment should be advisable for athletes that participate in sports where any form of head contact is common.

**Implications for acute recovery and long-term prevention**

The prevention being proposed is not what has been generally discussed (e.g. protective equipment, better techniques, improved medical supervision) which combine to provide a better environment for the athlete to offset potential long-term issues from concussive injuries. The prevention here relates to the concepts of
hydration and the impact that hydration has on the issues surrounding concussions and repetitive sub-concussive traumas. Instead, prevention is based on what we know about tau accumulation and inflammation in other diseases.9,42,68,74

First, we must examine what can we do once a head injury has been encountered to limit the effect of a head impact? This is where immediate evaluation of severity will be the best indicator for a time course for return to play.1,3,17,18,20 Generally, it is recommended that the athlete has to rest for a period of seven consecutive days, or until the athlete becomes asymptomatic and then slowly introduces light physical activity afterward. Following which engagement in four to seven days of light, physical activity should occur before the athlete can slowly reintroduce sport-specific training with typical recovery from a concussion being 14–20 days. However, there is limited empirical evidence to support such a position, especially related to introducing light physical activity for acute recovery or prevention of long-term impact.3,12,26,63,65,75–78 It must also be noted that during the acute recovery from head impacts, the focus of treatment should be on returning normal hydration within the tissues to minimize the compounding effects of the inflammatory biomarkers triggered by dehydration. The focus on rehydration will also provide mechanisms to clear the neurofilament fragments before they are able to form tangles and the tau or amyloid plaques. An issue that is problematic given travel and scheduling issues surrounding athletic competitions where head impacts can be regularly seen.

Additionally, there is an issue based on the alteration in fluid dynamics that can be problematic for younger athletes. As younger athletes may exhibit greater fluid shifts during activity because they have less total fluid available when compared to their older counterparts. A phenomenon that underpins the rationale for needing extended rest and recovery between athletic events for younger athletes relative to their older counterparts.47 Moreover, trauma to the adolescent or juvenile athlete may place them at higher risk for long-term issues relative to their adult counterparts.1,5,16,20,46,47 The recovery time necessary for the adolescent or juvenile is much longer than that for the adult and may take at least three weeks.46 Yet the scheduling of athletic events (practice or competition) may not be sufficient to allow for the necessary recovery, where the necessity for a long-enough period of recovery so as to allow for normal hydration to be reached or inflammation to subside is not met for the younger and less-experienced athlete. An issue especially important for these athletes is the impact that fluid shifts with trauma lead to reduction of CSF perfusion and secretion volumes leading to reduced CSF circulation. Whereby reduced circulation rate initiates a vicious cycle as changes in CSF perfusion that can trigger atrial natriuretic peptide (ANP) release, initiating the development of a deleterious feedback loop, in which increases in ANP induces additional fluid lost, that in turn triggers additional reductions in CSF that then triggers additional fluid loss and with reduced CSF an increased likelihood for amyloid accretion and accumulation.42,24,36,51,58 The unfortunate effect of this limited recovery may be one of the possible culprits for the high incidence rates reported for neurodegenerative disease among athletes that have an extensive history of participation in contact sports.17,19,21,66–68,70,73

Additionally, there are aspects of fitness that not only impact the likelihood for suffering concussive injuries but also impact the acute recovery allowing for return to play. Athletes who are active and hydrated appear to improve earlier in overall function and have a reduced recovery time due to earlier resolution of inflammatory signals acutely which may also reduce the long-term functional loss associated with concus-sive injuries.42,74,76,78,79 One investigation77 has directly shown that the level of fitness directly relates with the symptoms shown by an athlete following concussive injuries. While at the same time, other studies have both indicated that increased activity is safe and may assist in recovery from concussions.74,76,79 Factors that must be remembered in the development of fitness regimens meant to improve athletic prowess. As the training regimens may create athletes (especially those that are larger or participate in weight-class sports) that are unable to offset any degree of fluid shift that occurs during play. So training may not directly prevent the negative impact of head trauma, without regard to relative level of threshold imparted, from occurring. Yet, there is still the need to have athletes with a baseline fitness level that is adequate to minimize excessive inflammatory response and control fluid pressure changes associated with head trauma. A factor that is especially important when examined in the light of the prevalence for concussion issues among selective athletic populations (i.e. American Football) and where athletic events are being called into question and not the underlying physiological responses taking place within larger-bodied highly specialized athlete.21,67

Furthermore, changes in activity and hydration balance may also reduce the neurotransmitter imbalance seen acutely and lead to a normalization of mood and behavior, which can be coupled with the reduced inflammation leading to a “flushing” of the tau and amyloid proteins from the area of blockage.42 Increased activity also has been shown to reduce the risk for the health issues of overfatness57 that may compound the degeneration seen in the athlete with a history of head trauma coupled with poor resolution of injury and tissue hydration in the older (or retired)
athlete. As such, older and retired athletes should be encouraged to remain as active, if not more active, then when they were younger or competing in their sport of choice, thereby reducing the risk for chronic inflammation that is generally associated with overfatness. Additionally, increased activity will also increase thirst drive and require the retired (or older) athlete to increase fluid consumption and thus improve overall hydration status that would then assist with “flushing” of any possible tau or amyloid accumulation within the CSF.

Along with activity and consumption of fluids, there is growing evidence that nutrition (i.e. increase protein) and consumption of selective supplements (i.e. creatine) may aid in the recovery from concussion related to the issues associated with fluid balance. Based on the assumptions surrounding creatine monohydrate and tissue fluid shifts, supplementation of creatine following a concussive injury may be of benefit with re-establishing a euhydrated state within the tissues of the cerebral cortex. Additionally, the recommendations provided by the authors point toward changes in nutrition shifting metabolism within the neuron (and the body) to reduce oxidative stress (i.e. reactive oxidative species accumulation) that may be of benefit during the long-term recovery from a concussion or repetitive subconcussive injuries. As such, changes in nutrition (e.g. increases in creatine consumption) may not only reduce the acute symptoms, within the competitive season but may also assist in prevention of the long-term manifestation of loss, i.e. symptoms of CTE especially for those who are predisposed to neurodegenerative issues. However, the novelty of the research and limited body of evidence may limit the conclusions and recommendations being made from such studies, and more research is necessary to understand the mechanisms of action and overall role in prevention and recovery that is being purported.

Limitations

We are hesitant to be definitive in our remarks, as with any review, there are limitations that must be addressed. First of which, we are limited by the studies available for review. As indicated earlier, there were exactly zero studies that directly indicated that changes in hydration had directly caused either a concussion or the long-term issues from repetitive concussive and sub concussive injuries. Part of this limitation may stem from our methods of Boolean searching and may require subsequent searches utilizing a different set of parameters to directly address the question of interest here. Second, studies that have looked at hydration issues have examined whole body hydration level evaluation (as examined through USG measurements) and not hydration levels within the tissues. Thus, our conclusions are based more on deduction than inference from direct empirical evidence. Third, the ability to measure in real time, the impact of fluid shifts on concussions and cerebral functions presents a research dilemma for studying humans for a number of practical and ethical reasons. Last, there is the speculation made that cytoskeletal protein structures will undergo denaturing and dysregulation of repair in a similar fashion to proteins found within other tissues of the body prior to failure and injury of the tissue. A postulate that is especially important, given that issues of PCS and CTE are being diagnosed in populations that one would not expect to find it. Therefore, it has led us to surmise the underlying mechanism that hydration can play in explaining how trauma inflicted well below threshold might provide the initial step necessary for such diseases to be identified, even with a dearth of evidence. Yet we must remember that concussion and post-concussive issues are a multifactorial disease, and no single component can explain the issue in totality. Where future research should focus on addressing these limitations, as athletic populations are only one sub-set of the entire population where fluid shifts may subject them to an increased risk for concussion, PCS, or CTE.

Conclusion

Based on the various physiological responses, we can speculate that hydration has an impact on athletes for suffering concussive injuries and the long-term ramifications associated with sports-related concussive and repeated subconcussive traumas. This speculation can be distilled to three distinct factors of hydration that alter the susceptibility of concussive injury and long-term ramifications: (1) the athlete’s body composition, in particular level of fat mass reducing total water mass; (2) changes in inflammatory signals that impact resolution of injury promoting the onset of acute issues; and (3) alteration to normal membrane dynamics acutely that will ultimately impact the long-term issues associated with concussions and repeated subconcussive traumas (i.e. CTE).

These impacts can be summarized from three key perspectives of impact. First, changes within tissue hydration may limit the ability for neural and connective tissue to withstand concussive forces placed on the cerebral cortex during play. Even when forces are less-than-suspected thresholds for causing a concussion to occur, leading to greater risk for suffering a concussion. Second, dehydration at the time of injury may increase the biomarkers that trigger inflammation leading to the prolonged recovery following the onset of
acute issues (i.e. PCS). Additionally, dehydration may encourage the development of the tau and amyloid plaques that are linked with spongiform diseases associated with long-term issues (i.e. CTE). Last, there is a linkage between dehydration and inflammation that exacerbates the damage stemming from the initial trauma. The combination of factors that may explain why there appears to be a greater risk for a concussion and long-term issues within distinct populations indicated as having more susceptibility to dehydration issues (e.g. young athletes, female athletes, and athletes that are larger or overfat).

From these conclusions, we can indicate the following implications for athletes. Given the impact that hydration has on tissue damage, inflammation responses, and recovery, it may be wise to consider that additional recovery time may be necessary for individuals within distinct populations (e.g. those more susceptible to dehydration, younger athletes, less experienced athletes) where head trauma is a general risk during play. Additionally, the scheduling and travel ramifications of sports may increase the likelihood of combining dehydration with acute recovery from head injury. As such, it may be beneficial to examine the travel and scheduling of sports with known high levels of head impacts so as to minimize the compounding effects both acutely and chronically. For younger athletes, because of the interference that the combination of dehydration with trauma and inflammation can have on the normal growth and development, additional recovery time should be allotted between practices and competitions where head impacts have taken place that would increase the likelihood for resolution of any inflammation and ensure normal tissue hydration that might have been compromised due to the trauma and the exertion of play. Last, retired and older athlete need to remain active so as to offset any deleterious changes in health that might accompany a shift toward fatness signals accompanying a reduction in thirst and consumption of fluid that have been linked with increases in sedentary behaviors.

**Contributions**

Authors contributed to this publication as indicated: JEC and ES equally performed all tasks required for the review of materials included in the manuscript. Both were involved with editing the draft submitted. ES performed tasks related to the production of the manuscript related to the concussive events. JEC performed tasks related to the production of the manuscript regarding hydration’s impact on the concussive events and inflammatory responses.

**Data sharing statement**

There was no data involved in the production of the systematic review, where values have been shown the origin for the values have been credited back to the original sources.

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The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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