Treatment of Sports-Related Concussion

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Introduction

Sports-related concussion (SRC) or mild traumatic brain injury (mTBI) remains a significant healthcare concern for athletes of all ages. Clinicians and researchers are learning more details about the short- and long-term consequences of trauma to the brain. In 2012, the National Collegiate Athletic Association (NCAA) & the Department of Defense launched the largest study to date on concussion entitled the CARE Consortium. This research effort has yielded several studies advancing our knowledge across a spectrum of brain science in sports-related concussion.

The complexities of the pathophysiologic sequelae in the brain, combined with the clinical manifestation of behavioral signs and symptoms, are what can make the treatment of concussion challenging. Combine the difficulties in diagnosing and treating an athlete recovering from concussion with the pressure surrounding sports culture in America and you create a potentially dangerous environment for the concussed athlete. Moreover, there is an urgency to develop targeted treatments for young athletes as we are beginning to understand the correlations that exist between age of onset for sports-related head impacts and likelihood of repeat trauma [1]. Recent research into high school sports injury rates has revealed an alarming increase in the number of diagnosed concussions each year [2]. These young brains are in their formative years of neurological development and the long-term consequences from brain injury are significant.

In addition, there are tens of thousands of military personnel from multiple battle fronts overseas who have suffered traumatic brain injury and are in need of

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treatment and long-term care. This societal increase in brain injury rates has focused the research community's efforts into further understanding tenants of the brain's pathophysiological response to injury as well as short- and long-term clinical manifestations. However, researching effective treatments for mild traumatic brain injury meets with several challenges in forming evidence-based treatment approaches to improve patient outcomes and overall health [3]. Most treatment approaches remain grounded in the clinical domain of "functional recovery" while biomarkers of physiological recovery have not been made clinically meaningful. This intersection between functional and physiological recovery continues to demand our attention in order to maximize our outcomes and reduce the lifelong burden placed on quality of life following concussion.

Definition of Concussion

Reviewing the literature surrounding the treatment for concussion or mild traumatic brain injury (mTBI) requires that we examine the definition and events surrounding concussive injury. There is disparity among researchers on the issue of a unified definition of the term "concussion." The current accepted definition of concussion was re-tasked by the Concussion in Sport Group (CISG) during the first International Conference on Concussion in Sport in Vienna 2001 and has remained unchanged in subsequent examinations by the CISG. This group was comprised of researchers and clinicians from the fields of neuropsychology, sports medical physicians, neurologists, and neurosurgeons among other allied health professionals. These experts were highly involved in research as well as with the diagnosis, treatment, and management of sports-related concussion in patients. The CISG definition is as follows [4]:

"Concussion is defined as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. Several common features that incorporate clinical, pathological, and biomechanical injury constructs that may be used in defining the nature of a concussive head injury include the following:

1. Concussion may be caused by a direct blow to the head, face, neck, or elsewhere on the body with an 'impulsive' force transmitted to the head.
2. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously.
3. Concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than structural injury.
4. Concussion results in a graded set of clinical syndromes that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course.
5. Concussion is typically associated with grossly normal structural neuroimaging studies."

Although some medical experts and researchers vary in their approach to the term, in the research literature and in clinical terminology, sports-related concussion is often considered interchangeable with mild traumatic brain injury. In contrast to the CISG- based definition of concussion in 1993, the American Congress of Rehabilitative Medicine defined mTBI as a traumatically induced physiological disruption of brain function, as manifested by focal neurologic deficit(s) that may or may not be transient [5]. This contrasting definition is inclusive, in that mild traumatic brain injury involves some level of both functional and structural disruption to normal brain tissue that may or may not be permanent. The scope of this debate is beyond the intention of this chapter but considering the lack of a true clinical or research-based distinction between concussion and mild traumatic brain injury, the terms will be used interchangeably throughout the text of this chapter.

New Classification of Post-Concussion Syndrome

Athletes who suffer from sports-related concussion experience a variety of clinical symptoms caused by damage and neurologic dysfunction at the cellular level in the brain. Many of these individuals experience a recovery from clinical symptoms within 7–10 days post injury. However, several athletes recovering from sports-related concussion have clinical symptoms lasting 3 months or longer [6]. Formally, a diagnosis of post-concussion syndrome (PCS) is based on clinical symptoms defined by the *Diagnostic and Statistics Manual – Fourth Edition (DSM-IV)* as (1) cognitive deficits in attention or memory and (2) at least 3 or more of the following symptoms: fatigue, sleep disturbance, headache, dizziness, irritability, affective disturbance, apathy, or personality change [7]. In the updated *Diagnostic and Statistics Manual – Fifth Edition (DSM-V),* post-concussion syndrome is now diagnosed as neurocognitive disorder (NCD) of either major or minor classification due to the extent of traumatic brain injury. The specific DSM-5 criteria for neurocognitive disorder (NCD) due to traumatic brain injury are as follows [8]:

I. The criteria are met for major or mild neurocognitive disorder (decline in cognitive ability: memory, concentration, processing speed).
II. There is evidence of a traumatic brain injury – that is, an impact to the head or other mechanisms of rapid movement or displacement of the brain within the skull, with one or more of the following:
    - Loss of consciousness
    - Posttraumatic amnesia
    - Disorientation and confusion
    - Neurological signs (e.g., neuroimaging demonstrating injury; a new onset of seizures; a marked worsening of a preexisting seizure disorder; visual field cuts; anosmia; hemiparesis).
III. The neurocognitive disorder presents immediately after the occurrence of the traumatic brain injury or immediately after recovery of consciousness and persists past the acute post-injury period.

Biomechanics of Concussion

Acute concussion or mTBI is characterized by the disruption of neuronal homeostasis through physical forces transferred to the neuron through direct or indirect mechanical forces. The biomechanics of mTBI are important to understand when looking at the associated physiological damage that is created. These damaging forces include acceleration/deceleration, compression, and distraction or shear forces. Each of these forces creates a different signature within the brain and can have slight differing affects across the relatively isomeric characteristic of brain tissue. Each of these forces should be explored and defined, both singularly and in combination, as concussive injury to the brain. Rarely is brain trauma isotopic in nature (i.e., just stretch or just compression).

The acceleration force injury occurs when the head is fixed and is accelerated rapidly by an external force of an object colliding into it. These acceleration forces drive the inner cranium to collide with a fixed brain within the cranial cavity. In athletics, an example of an acceleration injury would be like the forces absorbed through punches being taken by a boxer or when a football player is "blindsided" by an opposing athlete and the head becomes violently accelerated. In contrast, the deceleration force is created when the head is already in motion and it is rapidly decelerated by a fixed object. A player's head coming into contact with the playing surface or with a fixed object on the playing field like a goal post would be an example of a deceleration force.

Acceleration and deceleration forces of a linear nature produce contusion-type injuries to the brain due to the absorption of compressive forces. A contusion located on the same side relative to the location of the applied external force is labeled a "coup"-type injury. A contusion received by the brain on a side opposite the side of the acceleration/deceleration forces is commonly referred to as a counter coup injury. The degree and depth of penetration for linear forces are modified by its intensity [9]. Mild acceleration/deceleration forces affect namely superficial layers in the brain. In addition, moderate-to-severe compressive forces can affect deeper structures within the brain. Thus, cell viability, structural, and functional disturbance of neurons can involve both cortical (superficial) and subcortical (deep) structures in the brain.

In addition to the damaging nature of linear acceleration/deceleration compressive forces, angular acceleration/deceleration stretches, or shear forces can generate significant trauma in the brain and are often considered more damaging [10]. These may be considered more damaging as the viscoelastic and gelatinous properties of the brain, with its subsequent high-water content, are highly resistant to compression and less resistant to distraction or shear tensile forces. These acceleration/deceleration forces contribute to the destructive distraction and shear forces or "stretch" on the white and gray matter of the brain. In addition, regardless of etiology, focal injury has a tendency to accumulate at the site of a transition in density as in the transition zones of gray matter (neuronal cell bodies) to white matter (neuronal axons), as well as along areas where vessels penetrate the gelatinous

matrix of the brain [11]. Angular acceleration/deceleration shear forces can create stretch injuries to the white matter or axons [12, 13].

Neurophysiologic Cascade of Injury

Seminal papers on the pathophysiology of concussion have been developed which have been foundational to our understanding of the traumatic sequelae resulting from the adverse biomechanical forces absorbed in the brain [14–16]. Researchers exploring treatment strategies base their interventions on the ensuing cascade of cellular events within the injured tissue in order to influence adverse effects downstream and ultimately limit the amount of damage to the brain. A brief overview of the different pathophysiological effects of concussion will be helpful as we describe the different treatment strategies outlined in this chapter and give context to the intervention.

Metabolic Dysregulation

Of the most damaging forces, stretch and shear strain forces applied to the neuronal cell body and axon, can cause significant membrane disruption with a cascade of neurometabolic events [17]. Disrupted membranes and altered membrane potentials result in a massive efflux of intracellular excitatory amino acids (EAA) and potassium (K^+) [18]. Additionally, mechanically induced depolarization contributes to the release of EAA-like glutamate. Once glutamate is released and subsequently bound, more intracellular K^+ is released compounding the distressed environment [19]. To restore intracellular homeostasis, the Na^+/K^+ ATP-dependent pumps work in excess [17]. This excess function demands increased amounts of ATP. However, the immediate ATP stores become quickly depleted, as normal oxidative metabolism of ATP is diminished and less effective glycolysis begins. This depletion of ATP available for the cell has been linked to mitochondrial dysregulation in the cell after mTBI [20].

Metabolic dysregulation mediated by compromised mitochondrial function also leads to a decreased glucose metabolic rate and depressed oxidative metabolism [21, 22]. This was primarily due to mitochondrial dysfunction and decreased respiration that is well documented in the literature after concussive injury to the neuron [22, 23]. DiPietro et al. developed a broader theory that the proteins associated with ATP-dependent processes within the cell and associated with the mitochondrial electron transport chain were downregulated at the time of injury as a form of "hibernation" state. It is theorized that this hibernation and hypometabolic state may be neuroprotective in nature and spare the cell from secondary metabolic cell death [24]. However, a prolonged state of metabolic dysregulation and hypometabolism may contribute to the deleterious long-lasting clinical features of minor/major neurocognitive disorder (NCD) often experienced in patients with prolonged symptoms [25].

Oxidative Damage and Apoptosis

The unregulated release of EAA contributes to an increased cellular concentration of Calcium. Increased amounts of intracellular Ca^{++} have direct and indirect consequences in the cell. A direct consequence of the cytosolic presence of Ca^{++} is the altered membrane potentials across the mitochondrial membrane [26]. Moreover, if not corrected, the increasing presence of Ca^{++} within the cell and within the mitochondria can stimulate the release of apoptic precursor proteins (Caspase 3). The indirect consequence of Ca^{++} accumulation in the cell is on the ATP-dependent voltage-gated Ca^{++} channels. This becomes another ATP-dependent process in the cell which requires energy. In the axon, Ca^{++}-mediated activation of catabolic enzymes will affect the cytoarchitecture in the effected microtubule, causing compaction [27]. In addition, Ca^{++}-mediated release of phospholipases works to disrupt cellular membranes of both the neuron and mitochondria, as they both have phospholipid bilayers regulating and protecting intracellular processes. Indirectly, glutamate induces neuronal cell death via stimulation of the N-methyl-D-aspartate (NMDA) receptor site. Through this action, extracellular Ca^{++} continues to enter the cell and activates Ca^{++}-dependent nitric oxide synthase, resulting in excessive nitric oxide formation. Production of free radicals combined with mitochondrial dysfunction, and the resultant upregulation of apoptic pre-cursor signaling proteins, can ultimately contribute to cell death [21, 25, 28, 29].

Among cells which remain viable, there has been some evidence of differential recovery of function between the soma (cell body) and axons of the groups of neurons exposed to injury [30]. The cell body has the density in organelles with the capability of earlier restoration of cell body homeostasis. This is in stark contrast to the axon, which has microtubule structures that are more vulnerable to the stretch and shear forces seen in mTBI. Through the stretch biomechanical forces absorbed, intracellular Ca^{++} stores are released, resulting in increased intra-axonal concentrations [31]. Dysregulation of resting membrane potentials across the axonal cellular membrane contributes to sustained heightened Ca^{++} concentrations, which contribute to secondary axonotomy in some stretched axons [31, 32]. This acute and sustained increase in Ca^{++} concentration leads to a cleaving of neurofilament side arms (leading to compaction) and microtubule disassembly [33]. The healing rates for axonal or white matter tracks can take days, months, or years according to diffuse tensor imaging research and delays in FA value recovery [30].

Inflammation

Neuroinflammation plays a role in neuronal cell death and regeneration and can be activated in mild TBI or concussion [34, 35]. Physical disruption of cellular membranes, unregulated excitotoxicity, altered cerebrovascular response, and mitochondrial dysfunction all contribute to the neurochemical milieu surrounding affected tissues and can contribute to neuronal injury and cell death. Neuroinflammation is characterized by activation of glia, microglia, and astrocytes

releasing proinflammatory mediators within the brain. These mediators subsequently recruit immune cells. Activation of the complement cascade and upregulation in the production of proinflammatory cytokines and chemokines define the neuronal inflammatory response and neuronal regenerative response in the brain [36]. This generalized response in the brain contributes to both cellular death and regeneration in the recovering brain tissue. Upregulation of proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and a subgroup of interleukins (IL-1, IL-6, IL-18) can facilitate the inflammatory response through activation of local microglial cells, as well as stimulating the expression of various endothelial cellular adhesion molecules (CAM) [37–41]. Cellular adhesion molecules are then responsible for local infiltration of neutrophils, leukocytes, and other inflammatory cells [42]. These neuroinflammatory changes occur in a dose response from repeated subconcussive blows and/or singular mild brain traumatic brain injury [43]. Moreover, these "subconcussive" exposures can trigger the same acute neuroinflammatory response, in the absence of measured behavioral changes, but are shown to increase infiltration of activated microglia/macrophages as part of the inflammatory response [43]. Neuroinflammation as described is a physiological process following concussive injury that can contribute to the cumulative and neurodegenerative effects stemming from repeated "subconcussive" and mild concussive injuries.

Cerebrovascular Response

In addition to the other cellular responses to injury, cerebral blood flow can also be compromised from mild traumatic brain injury [44–46]. Cerebral blood flow can remain compromised in the acute and chronic stages of recovery from mild traumatic brain injury [14, 47–52]. This is possible through uncoupling of the autonomic nervous system's ability to regulate heart rate based on vascular feedback loops from the sympathetic and parasympathetic nervous system [53, 54]. Local release of cytokines leads to perturbations in local perfusion rates within vascular beds surrounding lesion sites [55]. Moreover, these cytokines associated with neuroinflammation are strongly correlated to acute and chronic changes in cerebral blood flow [56]. Alterations in cerebral blood flow can last longer than 1 week in patients recovering from mTBI and can be significantly altered in patients suffering from chronic post-concussion syndrome [57, 58]. It has even been suggested that measurements of cerebral blood flow may act as a biomarker of recovery in athletes recovering from mild traumatic brain injury due the strong connection with neuroinflammation.

Ultimately, correction of these cellular dysfunctions lies in the brain's ability to restore adequate blood flow to the site of injury; restore/preserve cellular membranes; restore/preserve mitochondrial function; increase substrate availability; and limit the inflammatory response to cellular injury. As the brain restores homeostasis, the normal physiologic function of largely intact neuronal cells can remain disrupted.

Chronic Traumatic Encephalopathies

One area of increased attention over the past decade has been the "downstream" effects of repeated head impacts or traumas. These effects have both pathological and clinical features which, in some cases, can be fatal. These disease-states are the result of diffusely distributed neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, the presence of which ultimately disrupts neuronal function in the brain. It has been well established that brain injury, like what is experienced in sports-related concussion, is an environmental risk factor for acute and chronic tauopathy like what is seen in early onset dementia and Alzheimer's Disease [59]. One we hear about most often today is chronic traumatic encephalopathy or CTE. This pathology had been previously explored in the psychiatric literature and identified as "punch drunk" syndrome [60]. Its neuropathological features had been published recently and inform our current accepted features of the disease [61]. Furthering this association of repeated brain trauma and tauopathy was a landmark discovery of hyperphosphorylated tau with specific perivascular distribution reported by Dr. Bennet Omalu in the brain of a deceased football player [62]. Dr. Omalu reported these pathologies found in the brains of professional football players from the NFL who also demonstrated noted behavioral pathologies causing mental illness and ultimately leading to their untimely deaths. Today, CTE has a tissue presentation that is recognized as a distinct neurodegenerative disease neuropathologically defined by perivascular accumulation of abnormally phosphorylated tau protein at the depths of cortical sulci [63]. CTE, like many other taupathies, is attributed to traumatic brain injury stemming from subclinical to clinical head impacts [64].

The underlying mechanisms which ultimately lead to these disease states represent targets for therapeutic intervention which is currently ongoing. Proposed treatment strategies for sports-related concussion or mTBI and its physiological phenomena should attempt to address some of the deleterious pathophysiologic effects outlined above. Some attempts have been made to synthesize the literature to assess clinical *and* physiological features of injury and time course of healing to inform future directions in research on recovery from sports-related concussion [65]. At present, these serial biologic datapoints are not readily available and meaningful to clinicians. Therefore, this chapter provides a summary of the interventions currently being researched around mTBI using available definitions of functional recovery with some biological insight using imaging and animal models of mTBI to help inform the process.

Common Treatment Intervention Strategies

Review of the literature on treatment strategies being researched for sports-related concussion focuses on a few primary areas. Current treatment interventions receiving significant attention in the research include rest, exercise, physical therapy

interventions, and psychiatric/psychological interventions. We will examine the research surrounding each of these areas of rest, exercise, physical therapy, and psychiatric/psychological interventions.

Rest for Concussion

The long-standing recommendation of physical and cognitive rest has remained intact since the very first and subsequent concussion in sport group formed and provided concussion management guidelines [66–70]. Most recently, there has been a paradigm shift to introduce exercise or activity at an earlier stage of recovery following an initial period of rest [70]. The prescription of rest has been studied more closely by a few RCTs examining the recommendation and its effects [71, 72]. However, the major difficulties in validating this treatment recommendation across the body of research are largely due to the heterogeneity of research constructs. Attempts are being made to synthesize the information in a meaningful way so that clinicians can make evidence-based decisions for the use of rest and exercise in their treatment and management of athletes recovering from concussion [73, 74]. Prescriptions for *rest* studied in the literature are inconsistently assigned and result in varied timing of rest (i.e., acute vs. sub-acute); duration of rest; definition of rest; type of rest (cognitive vs physical); objective pre- and post-rest measures of "recovery" from concussion. The most glaring omission is the complete absence of neurophysiological biomarkers to assess tissue-based recovery in our patient population. We will attempt to summarize the *different* studies looking at *different* prescriptions of rest following concussion, demonstrating either a benefit, no benefit, or delayed "healing."

The research describing benefits of cognitive and/or physical rest are reported in the literature across decades of study [75–79]. In line with these findings are studies that describe patient prognosis when exposed to early cognitive stress. Dr. Gioia et al. found that school-aged students reported an increase in concussion-related symptoms when they were immediately returned to school [80]. In a prospective cohort study, early cognitive rest was supported by Dr. Brown and colleagues [81]. Brown et al. determined that increased cognitive activity was associated with longer recovery from concussion and therefore supported the idea of early cognitive rest. In addition, a recent study by clinicians at a concussion treatment clinic found that a 7-day period of rest prescribed during *any* phase of recovery post concussion significantly improved cognitive testing measures and symptom reports across high school- and college-aged athletes [78]. Even more, Gibson et al. found no association with early cognitive rest to the duration of symptoms in athletes evaluated and enrolled in a sport concussion clinic [82]. As a result, it is still recommended that adolescents recovering from sports-related concussion have a *brief period*, typically 24–48 hours, of cognitive rest designed to reduce cognitive burden on the brain in order to support recovery and full return to academics [83–87].

Early Activity or Exercise for Concussion

As noted in an earlier section, concussion happens when traumatic forces cause a cascade of physiological effects on the brain. As such, the clinician and guiding physician treating athletes recovering from concussion should employ strategies that look to counteract these damaging physiological effects. In a broad sense, one such strategy has emerged over the past decade: activity or exercise. The health benefits of early movement and exercise following concussion have been reported in the research for decades [88]. Chronic exercise is noted to improve overall function in the brain and specifically clinical outcomes from a wide range of mental illness [89], brain disease [90, 91], cognitive function [92], and trauma [93]. Exercise and acclimation to environmental stresses enhance several neuroprotective mechanisms in the brain [94] and subsequently make the brain more resilient to disease and injury [95, 96]. As such, the prescription of exercise for athletes in their recovery from sports-related concussion is a practical application of the large body of literature for the improvement of patient outcomes in concussion.

In contrast to the previous section, a growing body of research has found no direct benefit from a prescription of rest or *prolonged* rest [88, 97–99]. Moreover, in a recent meta-analysis of RCTs for rest & aerobic exercise, researchers found that protocols that included a normal rest period contributed to longer recovery times and higher symptoms scores on PCSS [100]. Examining the effects of early activity, one study by emergency room physicians assigned patients to either 5 days or 1–2 days of rest followed by a gradual return to activity. The clinician researchers found that rest for 5 days vs. 1–2 days resulted in a larger number of reported symptoms by patients [101]. Confirming this finding, Howell et al. found that athletes who engaged in aerobic activity within the first week post-concussive injury reported lower symptoms severity than their non-exercising peers [102]. Wilson and colleagues also found that children and adolescents recovering from concussion who engaged in early activity report fewer and milder post-concussion symptoms and recovered sooner than their peers who were prescribed relative rest [103]. Translational research using animal models of concussion shows that immediate activity following brain injury upregulated genetic transcription factors supporting healing as well as improved behavioral activity scores in mice [104]. Combined, these findings of benefits *and* non-benefits lead us to the conclusion that this area of initial care using rest needs further investigation to fully understand what clinicians should be prescribing for their athletes recovering from concussion.

As with most areas of promise in the treatment of brain injury, its application remains limited to the objective measures of functional injury resolution. Clinicians still lack the ability to assess physiologic recovery and tissue recovery objectively through readily accessible and relevant biomarkers. So, we will examine the effect that exercise has on the recovering brain through that lens. From the animal and human imagining and physiological research, we can examine how exercise improves overall brain physiology and function in the specific areas effected by sports-related concussive injury.

Neurophysiologic Adaptation to Exercise

Neurovascular Response to Exercise in Concussion

Additionally, it is well known that the vasculature in the brain changes with exercise [105]. Exercise is capable of new vascular formation in the cerebral cortex [106] and strengthening cerebrovascular reactivity [107]. These changes due to exercise positively affect the brain and help to mitigate the strength of negative vascular responses post injury as sports-related concussion causes acute and chronic cerebrovascular reactivity and hypoperfusion [57].

It has been demonstrated that exercise as a treatment modality can restore normal perfusion in the brain to areas previously effected [57]. Exercise has been proven to improve and promote cerebrovascular circulation through reperfusion and angiogenesis in the brain. During exercise, the brain becomes "flush" with heavily oxygenated blood. While humans exercise, the brain is challenged with providing the musculoskeletal system and body organs with an adequate amount of blood to meet the increased metabolic demands. In addition, the body must maintain adequate arterial blood pressures across the entire system. Compared to the dramatic increases across the periphery and organs, the increase in cerebral blood flow is only mild (<30% increase in CBF) up to ~60% Max VO2 [108, 109].

Research looking at patients with chronic post-concussion syndrome has shown differences in cerebrovascular blood flow compared to normal controls in pediatric and adult populations [48, 57, 58, 110]. Consequently, when exercise is prescribed for athletes recovering from concussion, researchers have found restoration of CBF and improved tolerance to exercise [57, 111].

Neuroplasticity, Neurogenesis, and Exercise

Exercise, in particular aerobic exercise, has a long line of research demonstrating its benefit on the improvement in neurogenesis, cognitive function, and plasticity [112–116]. The processes that support these functions also promote healing as the brain recovers from trauma. Exercise enhances the production and release of several factors in the brain and from the periphery, including substances like BDNF, IL-1, VEGF, and lactate, all of which have been indicated in neuroprotective cascades in the brain. Briefly, brain-derived neurotrophic growth factor (BDNF) is believed to be a major factor in hippocampal function, neuronal cell survival, synaptic plasticity, neurogenesis, and mitochondrial biogenesis [117, 118]. Insulin-like growth factor 1 (IGF-1) is a neurotrophic hormone taken up by the brain after exercise. IGF-1 interacts through many complex pathways to promote amyloid β production and the stabilization or preservation of synaptic plasticity in recovery from brain injury [119]. Moreover, studies of exercise following brain injury demonstrated early uptake of IGF-1, which reduced overall brain lesion size [120]. Vascular endothelial growth factor (VEGF) is a cytokine responsible for the restoration/promotion of new blood vessels and long-term potentiation in the brain. Exercise upregulates the

production of VEGF in the brain which subsequently works counter to the localized compromised regional cerebral blood flow seen in mTBI through angiogenesis [121]. Finally, lactate is a by-product when pyruvate is broken down by muscle during moderate activity. When its produced at a faster rate that it can be processed, lactate concentrations remain elevated in the blood. This increase in blood lactate is utilized across the body and is also taken up in the brain to support various functions during exercise [122]. Lactate is also used as an energy substrate for neurons recovering from TBI [123]. In addition, lactate is also closely linked with increased VEGF production by binding to lactate receptors in the brain [121].

Mental Illness, Concussion, and Exercise

Over the past decades, exercise has long been prescribed to improve outcomes from patients with mental illness across a spectrum of disorders [124–135]. Trauma-enhanced mental illness is a serious growing public health crisis where adolescent and adult athletes sustaining concussion have an increased susceptibility [136–139]. Moreover, many parents of adolescent patients recovering from concussion are not fully aware that they need diligence in identifying mental health-related symptoms following concussion [140]. Population- based research tells us that school-aged adolescents sustaining a concussion have an increased risk of poor mental health outcomes that includes increased or persistent depression symptoms including attempted suicide [141–144]. This is also supported in research on adults suffering multiple concussions that demonstrate an increase in impulsivity and aggression [145] and symptoms of mental illness like anxiety and depression [146, 147]. The prescription of exercise for the subgroup of concussion with mental illness has demonstrated promising findings.

Exercise, Heat Acclimation, and Neuroprotection

As regular exercisers, athletes have developed many physiologically adaptive responses to stress. One of those areas of stress comes from the environment. Research in the area of heat stress and acclimation during exercise has yielded insights into proposed mechanisms of neuroprotection and neurophysiological adaptation. The brain's adaptations to heat stress may indirectly influence how the brain responds to the added condition of trauma. Known adaptations to heat stress in the areas of vascular response and, more specifically, the upregulation of heat shock proteins are discussed in this section.

As discussed in the previous section, exercise up to 60% VO2 increases global CBF by as much as 30% above which point CBF is maintained or reduced, despite the continued cerebral metabolic demands that often are enhanced during exercise. The introduction of heat stress during moderate-to-heavy exercise enhances the uncoupling between metabolic demands and a subsequent reduction in CBF [148]. In addition, the cerebrovascular demand across the brain is regionally modified in

an attempt for the brain to address location-specific activation, which may be compromised in the heat. It has been demonstrated in the literature that anterior hemispheric CBF may be compromised or reduced during exercise in the heat [149]. Therefore, under hyperthermic conditions, this "pre-existing" increased metabolic demand and lowered regional blood flow may in some way contribute to worse outcomes, although it has not been directly assessed in animal models of hyperthermia and concussion [150]. This remains a hypothetical framework that has not been investigated fully.

Animal models and human case studies of heat stress and trauma have given us insight into the underpinnings of worse physiological and clinical outcomes following mild-to-moderate TBI [150, 151]. The brain's ability to preserve brain function and mitigate the stress of heat may be largely modulated by the expression of a group of stabilizing proteins called heat shock proteins. Research in the area of neurophysiological acclimatization to heat has focused on the expression of these heat shock proteins and their role in stabilizing intercellular processes during times of stress and heat induction. These proteins contribute to the local intra- and extracellular environment both directly through stabilization of cellular proteins and indirectly through the up- or downregulation of cytokines responsible for apoptosis, tau protein toxicity, and amyloid plaque formation. This cellular response to heat stress is seen across many tissue and cell types. There are some sub-families of heat shock proteins present in the brain which can provide neuroprotective effects. However, to date, there are no published studies that examine the effects of these sub-groups of heat shock proteins and their effect on mechanically induced neurotrauma (i.e., concussion).

We can however describe the peri- and posttraumatic hyperthermic environment under which these heat shock proteins may play a role. Some sub-families of heat shock proteins and their subsequent functions are described. Heat shock transcription factor-1 (HSF-1) is a precursor for heat shock protein-1 (HSP-1). Its primary role serves in the stabilization of endoplasmic reticulum function and the downregulation of certain proapoptic cytokines [152, 153]. It also supports mitochondrial and cellular function through the preservation of intracellular protein folding within the endoplasmic reticulum. In general, this would assist neurons in the restoration of cellular homeostasis if these proteins and mechanisms are active during mechanically induced neurotrauma.

Heat Shock Protein-27 (HSP-27) is a protein which can have neuroprotective effects against tau protein toxicity. In mTBI, early mechanisms following trauma result in hyperphosphorylated tau. This overexpression of these specific proteins forms neurofibrillary (NF) tangles, which disrupt normal cell function in the brain and can lead to early onset dementia, Alzheimer's, and ultimately, cellular apoptosis. HSP-27, along with other proteins expressed in the astrocyte, has a neuroprotective effect on tau phosphorylation [154]. This decreased expression of tau has the potential to protect against the long-term formation of NF tangles as a result from trauma.

Finally, heat shock protein-70 (HSP-70) has been reported in the research to have a potentially therapeutic effect for patients with Alzheimer's disease (AD). The

presence of amyloid plaques in the brain is a result of the overexpression of β-amyloid peptides through beta-amyloid precursor protein phosphorylation. Like the production of NF tangles, β-amyloid plaque deposits disrupt the normal cellular function of neurons and astrocytes in the brains of patients diagnosed with Alzheimer's disease. Both NF tangle and amyloid plaque formation have been the target for research aimed at treating AD. Hoshino et al. focused on the expression of HSP-70 in transgenic mice. Mice with an increased expression of HSP-70 were able to decrease the production of β-APP through decreased expression of β-amyloid-degrading enzymes and TGF-β1, which is a cytokine that stimulates phagocytosis of β-APP [155]. TBI also stimulates the production of β-amyloid plaques. In a sense, an active expression of HSP-70 through heat acclimation training may have a potential benefit in the long-term formation of these damaging plaques.

Heat shock proteins along with other proteins and cellular components can potentially play an important role in the preservation of homeostasis to the injured neuron. It certainly appears that heat shock proteins have a neuroprotective effect as it relates to both the short- and long-term consequences of neuronal stress under controlled conditions. Research in this area using animal models of injury may provide a clearer picture of the functional role these proteins play in preservation of neurons as result of trauma under hyperthermic conditions. These claims of hyperthermia-induced physiological changes have not been substantiated in the research and are therefore a hypothetical framework of neuroprotection in mTBI.

Psychological Treatment of Concussion

Increasing attention has been given to mental health disparities occurring secondary to sports-related brain injury. It is widely accepted that psychological treatment techniques like psychoeducation, cognitive behavioral therapy (CBT), and mindfulness-based treatment techniques are an effective treatment option to improve executive function, reduce PCSS scores, improve quality of life, and reduce symptoms of depression and anxiety in mTBI patients [156, 157]. This section reviews the research surrounding these psychological treatment strategies and their efficacy.

Psychoeducation

There is some evidence to support the use of early psychoeducation about expected post-concussive symptoms and recovery from concussion. Several studies providing early reassurance regarding expected recovery, guidance about managing symptoms, and guidance in resuming pre-injury roles in the acute phase of injury found a significant effect of reported symptoms 3 months later [158]. Minderhoud and colleagues provided patients with a manual on the nature and recovery of symptoms seen in PCS and found significantly reduced reports of PCSS 6 months post injury [159]. In two different studies where patients were

issued a manual or pamphlet specifying what symptoms to expect and how to manage symptoms and stress, the patients claimed that the information helped, or they reported fewer symptoms [158, 159]. This trend of reduced symptom reporting has shown up in several other studies involving early psychoeducation as well. This would indicate that early psychoeducation does not prevent the development of symptoms, but rather facilitates better coping strategies and symptom management. This is exactly what Wade and colleagues concluded in their study [160]. They provided patients with an informational sheet about potential symptoms and additional clinical support as needed, but found no objective difference in symptom severity at 6 months post injury. They did, however, find significant improvement in daily functioning and activity [160]. In 2002, Ponsford and colleagues provided patients with a pamphlet on potential symptoms and coping strategies [161]. They found almost identical results to those of Wade with no significant improvements on neuropsychological assessments, but significantly fewer symptoms reported by the treatment group when compared to controls [161]. This is not to say that early education does not have a place in treatment of concussion. It has long been established that patients' appraisal of recovery can have a strong effect on their rate of recovery and overall perceived quality of life. Furthermore, it has been shown that stress can exacerbate concussion symptoms and slow recovery; therefore, early education may be beneficial simply by helping to foster management of symptoms and stress [162]. The inclusion of early education practices in managing patients recovering from concussion is indicated to manage injury-related stress.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) takes the results of early education and improved symptom coping and management and attempts to apply them to individuals suffering from PCS. Cognitive behavioral therapy targets individuals' maladaptive beliefs, emotions, and cognitive processes [163]. In PCS populations, CBT seeks to improve the emotional appraisal of symptoms, coping, and stress management following injury. In a meta-analysis of RCTs, there were positive effects of cognitive behavioral therapy on sub-acute depression and anxiety scores [157]. In studies of individuals with head injuries, subjects often underestimate the frequency and severity of PCS-like symptoms pre-injury. Comparatively, healthy controls were better able to predict or anticipate potential symptoms of PCS. This difference in perception and expectation of injury can lead to cognitive bias and result in focusing on and exacerbation of symptoms. It has also been found that negative causal attributions and expectation predict persistent symptoms 3 months post injury [163]. Whittaker, Kemp, and House found that patients who expected serious negative consequences were more likely to have persistent symptoms [164]. They also found that severity of injury and symptoms did not better predict persistent symptoms than negative expectations [164]. In pediatric populations, CBT has been used to treat those with prolonged recovery trajectories and improve their ability to

cope with and reduce PCS symptoms burden, reduce sleep disturbance, and improve mental health symptom reports [165–168].

Although there are limited studies on maladaptive behaviors and coping in concussed individuals, some studies of more severe TBI have shown that poor coping and maladaptive behaviors such as self-blame and symptom focusing have been associated with worse outcome. It is believed that maladaptive behaviors and perceptions may contribute to the maintenance of PCS and PCS-like symptoms.

Mindfulness-Based Stress Reduction

Mindfulness-based stress reduction (MSBR) is another psychological treatment that focuses on the management of negative thoughts, emotions, and behaviors. It involves mind-body-focused practices such as yoga and meditation that are intended to make one more aware of their internal state and resources. A review of the research on mindfulness techniques shows improvement in function of various structures in the brain and improved functional connectivity across the default mode network (DMN) [169]. Mindfulness-based stress reduction, like other psychological intervention platforms, aims to combat the effects of stress, anxiety, and depression that sometimes accompany mTBI post-injury symptom cluster.

Earlier this decade, research using MSBR in mild-to-moderate TBI patients had produced inconclusive results with regard to objective improvements. One study using a mindfulness-based stress reduction intervention on TBI patients produced no real treatment effect [170]. McMillan and colleagues found no significant effects on objective or subjective measures of cognition, mood, or symptom reporting in a cohort of TBI patients [170].

In a more recent growing body of research, many clinicians are reporting positive interventions from mindfulness-based treatment. In two studies from Bedard and colleagues, they used MBSR interventions at a frequency of one session per week for 8 weeks and demonstrated statistically significant improvements in depression symptoms, reduced pain intensity, and increased energy levels [171, 172]. However, like most of the mindfulness research, it should be noted that Bedard had a small sample size and the MBSR intervention was used as a supplement to another group-based treatment plan; therefore, its result cannot solely be attributed MBSR intervention.

In another small cohort of military mTBI patients, researchers used mindfulness-based classes that met weekly to treat a group of servicemen who reported lingering cognitive effects of concussion 1 year post injury [173]. Treatment using MBSR resulted in fewer reports of cognitive symptoms and lower symptoms associated with PTSD. In a pilot study of MSBR in treating post-concussion syndrome, patients were led by neuropsychological experts trained in MSBR for a 2-hour session once a week for 10 weeks [174]. The study found significant changes in perceived quality of life and self-efficacy, but no significant improvements in symptoms [174]. Similarly, in a study of patients recovering from mild-to-moderate TBI, researchers looked at measures of chronic stress, PCSS, and depressive

symptom reports [175]. They reported MSBR reduced chronic stress reports as well as PCSS and depressive symptom scores compared to the active control group. Additionally, Polich and colleagues studied focused attention meditation and a form of mobile neurofeedback in mild-to-moderate TBI patients and discovered an overall reduction in symptom report and anxiety/depression inventory scores [176]. These positive trends are also demonstrated among pediatric mTBI cohorts using MSBR treatment techniques [177].

It would appear that MSBR helps patients to cope with reported symptoms and improve overall mental health recovery following brain injury. Mindfulness-based therapy may be used in conjunction with a treatment plan that provides objective scoring measures that assess mental health status following mild traumatic brain injury.

Conclusion

While great efforts have been made to advance the treatment options for individuals suffering from a concussion or mTBI, there is still no standard of care. This is partly due to the individualized approach many clinicians take, tailoring to the needs of the specific individual. As the knowledge of the physiology of concussion continues to grow, this will further help to develop treatment plans that are scientifically backed and can be tailored to an individual post injury. While rest, exercise and physical activity, and psychological approaches were discussed at length here, various technologies, supplements, and other therapies are being explored for their potential utility in individuals suffering from concussion. Many of these are in the preliminary stages of research and more work is needed to determine their effectiveness to be able to offer individuals suffering from concussion valid, effective, and individually tailored treatment options.

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