# The collective therapeutic potential of cerebral ketone metabolism in Traumatic Brain Injury

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**ABSTRACT (200words max)**

The post-injury period of glucose metabolic depression is accompanied by adenosine triphosphate decreases, increased flux of glucose through the pentose phosphate pathway, free radical production, activation of poly adenosine diphosphate ribose polymerase via DNA damage and inhibition of glyceraldehyde dehydrogenase (a key glycolytic enzyme) via depletion of the cytosolic nicotinamide adenine dinucleotide pool. Under these post-brain injury conditions of impaired glycolytic metabolism, glucose becomes a less favorable *energy* substrate. Ketone bodies are the only known natural alternative substrate to glucose for cerebral energy metabolism. While it has been demonstrated that other fuels (pyruvate, lactate and acetyl-L-carnitine) can be metabolized by the brain, ketones are the only endogenous fuel that can contribute significantly to cerebral metabolism. Preclinical studies employing both pre-and post-injury implementation of the ketogenic diet have demonstrated improved structural and functional outcome in traumatic brain injury models, mild TBI/ concussion models, and spinal cord injury. Further clinical studies are required to determine the optimal method to induce cerebral ketone metabolism in the post-injury brain, and to validate the neuroprotective benefits of ketogenic therapy in humans.

Nationally, the incidence of traumatic brain injury (TBI) exceeds that of all other health diseases with an annual incidence of 1.7 million new cases(1). It is an injury that affects both genders across all age groups, producing long-term disabilities that negatively impact families and society. Recent years have seen a substantial increase in public awareness of the long-term cognitive, emotional and functional consequences of TBI. However, several potential neuroprotective treatments such as therapeutic hypothermia have produced disappointing results when tested in the clinical setting (2, 3). Thus there is a significant need to identify better strategies to improve global outcome after TBI. In addition, given the inherent differences between the developing brain in which dynamic processes such as synaptogenesis, myelination and plasticity are ongoing, and the mature adult brain in which these processes have been completed, any potential neuroprotective treatment must be evaluated in an age-specific manner. To that end we discuss the changes in cerebral glucose metabolism, which have been described in the aftermath of TBI, the age-related variation of this metabolic dysfunction, and the potential of using the natural ketone metabolism mechanisms to ameliorate these problems and improve global outcome.

## METABOLIC DYSFUNCTIONS AFTER TRAUMATIC BRAIN INJURY

Upon impact, rapid movement of the brain within the skull initiates a series of neurochemical disruptions that alter cerebral metabolism. Within minutes after injury, the ionic equilibrium across the neuronal membranes is disrupted, with injury severity-dependent increases in the concentration of extracellular potassium and glutamate as well as intracellular calcium accumulation (4, 5). This disruption of ionic equilibrium requires cellular energy to re-establish homeostasis, which is reflected by increases in cerebral glucose uptake observed within 30 minutes after adult rodent fluid percussion injury (6) and within 8 days after human TBI (7).

This transient increase in glucose uptake is also known as "hyperglycolysis" and is followed by a prolonged period of glucose metabolic depression. These cerebral metabolic changes are a hallmark response described in both experimental and clinical brain trauma. $^{14}$C-2-deoxy-D-glucose autoradiography studies in adult rats following fluid percussion (FP) or controlled cortical impact (CCI) injury both show significant ipsilateral decreases in the cerebral metabolic rate of glucose (CMRglc) lasting 7-14 days depending on injury severity. Similarly, $^{18}$F-deoxyglucose PET studies in human patients also reveal long-term glucose metabolic depression after TBI. Experimental studies have shown that the magnitude and duration of the glucose metabolic depression increases with injury severity and age (8–10).

The duration of CMRglc depression increases from 5 days in adult mild FP injury to 14 days in severe FP injury (10). The FP model generates a more generalized concussive injury, whereas the CCI model produces a more severe injury with a predictable cortical contusion. Corresponding to this increased severity, a greater magnitude and duration of glucose metabolic depression are observed with the CCI injury model (11, 12). In human TBI patients the level of consciousness (as measured by Glasgow Coma Scale) shows significant correlation with CMRglc in thalamic, brainstem and cerebellar structures (13).

The duration of post-TBI CMRglc depression also increases with cerebral maturation. Postnatal day (PND)17 rat pups given the same FP injury as adult rats showed faster recovery (3 days) of CMRglc depression (9). Adolescent PND35 rats showed earlier recovery of glucose metabolic rates in subcortical structures than adult PND90 rats (12). In general, animal models have demonstrated age-dependent recovery of CMRglc after TBI, but comparison of glucose metabolic recoveries after TBI within the human pediatric population have not yet been studied.

Other biochemical changes, which occur in the aftermath of TBI, further disrupt glucose uptake and metabolism. For instance, proton NMR spectroscopy of [1,2 $^{13}$C] labeled glucose demonstrates a 9-12% increase in glucose processing through the pentose phosphate pathway between 3-24hrs after CCI injury, thereby decreasing the available glucose supply for energy production (14). TBI also has been shown to generate early increases in reactive oxygen species (ROS) which damage lipids, protein and DNA (15–19). ROS-induced DNA damage activates DNA repair enzymes, such as poly-ADP ribose polymerase (PARP). In the presence of DNA strand breaks, pathological activation of PARP depletes cytosolic nicotinamide adenine dinucleotide ($NAD^+$), which ultimately inhibits glycolytic processing of glucose at the glyceraldehyde phosphate dehydrogenase step (20). Collectively these series of biochemical changes divert and obstruct processing of glucose through the glycolytic pathway. The consequent decrease in glucose oxidation and ATP concentrations (21, 22), make glucose an inefficient energy substrate in the post-TBI brain.

## KETONES AS ALTERNATIVE SUBSTRATE EARLY AFTER TBI

Cerebral ketone metabolism has been demonstrated to contribute significantly to brain metabolism under various conditions of energy challenges (23). Observations that suckling rats, who rely upon ketone bodies in addition to glucose as necessary metabolic substrates (24, 25), recover metabolically and behaviorally faster than adults following TBI led to the idea that alternative substrates may be protective (9). Utilizing cerebral ketone metabolism as a therapeutic approach is not only appealing because it can bypass the early glucose metabolic derangements after TBI, but it offers numerous other consequences that are beneficial after brain injury (Figure 1). Ketone bodies require only 3 enzymatic steps to enter the TCA cycle, have

been shown to improve metabolic efficiency (26–28) and increase the ΔG' of ATP hydrolysis (29). Ketone metabolism can also decrease the production of free radicals in both the mitochondria and cytosol (30–32). The multiple target action of ketones makes it a powerful tool in injuries that activate a multitude of cascades simultaneously and consequently there has been an increasing number of studies which demonstrate beneficial consequences of the ketogenic diet, calorie restriction and fasting after brain trauma.

One of the earliest studies exploring the potential use of alternative metabolic substrates following TBI demonstrated that intravenous infusion of $^{14}$C-3-ßHB three hours following CCI injury in the adult rat resulted in greater cerebral uptake of ßHB with greater production of $^{14}CO_2$ (33). The increase in ketone metabolism improved regional ATP concentrations, demonstrating the potential for alternative substrate therapy after trauma. To avoid the plasma osmolarity changes associated with long-term intravenous ketone infusions, subsequent studies utilized a 4:1 ketogenic diet (Bioserve F6666). The high fat, low carbohydrate ketogenic diet is already clinically established as a treatment for pediatric epilepsy (34). The strength of diet therapy is measured by the ratio of grams of fat: carbohydrate + protein, with the "dose" typically ranging from 1:1 to 4:1. In contrast, a standard American diet is roughly equivalent to a 0.3:1 diet ratio (35). Variations of the ketogenic diet have been administered after TBI to induce early ketosis. When the ketogenic diet was given to postnatal day PND17, 35, 45 and 65 rats after CCI injury for 1 week, an age-dependent neuroprotective effect was observed (36). PND 35 rats (analogous to an adolescent age group) fed the ketogenic diet had increases in plasma ßHB levels within 6 hrs, which was sustained for the week (36, 37). However, plasma ketone levels did not increase until 24 hrs post injury in adult rats. Ketone metabolism significantly decreased lesion volume and number of degenerating fluoro-jade positive cells in PND35 and 45 rats, but not in the

younger or older age groups. The same ketogenic diet given immediately after CCI injury for 1 week also showed improved motor and cognitive function in the PND35 age group (38). The PND35 rats on the ketogenic diet showed significant reduction in number of hindlimb footslips off the beam walking task and showed shorter latencies in the Morris water maze relative to adult rats. Age differences in metabolic responses to the Bioserv F6666 ketogenic diet were also observed after TBI. Cortical tissue from PND35 rats on the ketogenic diet after CCI injury had improved ATP, creatine and phosphocreatine levels and normalization of NAA and lactate levels at 24 hrs post injury, which were not observed in adult ketogenic diet rats (39). Administration of this diet immediately after CCI injury has been shown to have age dependent effects of CMRglc changes, with the ketogenic diet further reducing TBI-depression of CMRglc in adolescents to a greater extent than in adults (12).

The age difference in uptake of ketones (as reflected by the decrease in glucose uptake) may reflect either actual differences in transporters or differences in timing of plasma substrate increases. In fact, both may play a role in the efficacy of ketones in mitigating TBI induced cascades. Cerebrovascular expression of monocarboxylate transporter (MCT) 1 and 2 are increased 80-88% greater in microvessels from CCI injured PND35 rats compared to CCI injured adult rats, which may enhance cerebral uptake of ketones after injury (37). However, the time course of plasma ketone concentrations is delayed in the adults, which may delay the ability of cerebral ketones to counteract ongoing pathological processes. While intravenous administration of ß-hydroxybutyrate could be an alternative approach, fasting for 24hrs has been shown to increase plasma ketones and elevate MCTs in the adult brain (40). Given the rapid pathological progression following TBI, alterations that increase ketone availability and delivery could help resolve this issue.

The 4:1 ketogenic diet (Teklad 96355) has also been used to reduce cell loss after weight drop injury (41, 42). In these studies PND35 rats were placed on the ketogenic diet immediately after injury and edema and apoptosis were quantified. Animals on the ketogenic diet showed decreases in the Bcl-2-associated X protein (Bax) mRNA (48%) and protein (44%), which blocking the anti-apoptotic Bcl-2 protein and decreases cellular apoptosis (30%) and brain swelling (1%). Animals on the ketogenic diet also showed decrease in mitochondrial release of the electron transport enzyme, cytochrome c, into the cytosol. Normally this action initiates apoptotic signaling cascades, which are inhibited by cerebral ketone metabolism.

In addition to the CCI and weight drop models that produce evolving contusions, the ketogenic diet has also been used after a concussive fluid percussion (FP) brain injury. PND56 rats were given FP injury 3 weeks after the standard or ketogenic diet (Bioserv F6666) was initiated to test the seizure threshold (43). Animals on the ketogenic diet showed longer latencies for flurothyl-induced seizures and had less hippocampal cell loss than standard fed FP injured animals. Collectively, ketosis induced by the ketogenic diet has been shown to confer neuroprotection after various types of TBI in the adolescent/young adult rat.

Induction of ketosis via fasting has been shown to provide protection from brain injury in adult animals (44). Fasting adult rats for 24 hrs increased cortical tissue sparing, decreased markers of oxidative stress and decreased mitochondrial calcium loading after moderate CCI injury, but not after severe injury. Interestingly, animals fasted for 48 hours did not show significant cortical tissue protection. Despite the fact that fasting induced ketosis 24 hours post injury, a protective effect was still observed in the moderately injured adult animal. At this time the interaction between injury types, severity, age and type of ketosis induction remain unclear.

## KETONES AND CONCUSSION

Concussion awareness has increased in the national media, bringing new attention to the milder forms of TBI. Concussive brain injuries have been shown to produce similar metabolic pattern of derangements, but with faster recovery than severe injuries. A closed head injury model developed to deliver a concussive injury to the adolescent rat brain reveals that even an injury that produces no cell loss, contusion, or bleeding results in measurable period of decreased CMRglc (45). PND35 rats given a single concussive injury showed recovery of cortical metabolic rates between 3-5 days post injury. Introduction of a second concussion during the metabolic recovery of the first injury results in prolonged CMRglc depression. These results indicate the cumulative nature of concussive injuries and emphasize the significance of the state of brain metabolism after injuries. There is evidence that administration of the ketogenic diet immediately after the first concussive injury improves cognitive function after the second concussive injury (46). PND35 rats given 2 concussions separated by 24 hours show significant deficits in the novel object recognition task when tested 1 day after the last injury. However, animals that received the ketogenic diet for the 24hr interval between the 2 injuries visited the novel object first and spent more time with the new object, showing better cognitive performance. The effects of ketones administration prior to repeat mild TBI has also been recently examined in adult rats (47). Standard diets supplemented with 6% fish oil were given for 4 weeks prior to repetitive FP injury. Animals were maintained on the diet for another 2 weeks post-injury before undergoing Morris water maze testing and histological assessment. Adult rats given the modified omega-3 fatty acid diet showed improved cognitive performance.

The usefulness of ketogenic therapy in concussive injuries needs to be further studied, but the idea is already gaining attention (48). This year two clinical trials examining the

effectiveness of omega-3 fatty acids on sports related concussions in Division I National collegiate athletic association (NCAA) athletes (49, 50) and children (51). The concept of utilizing alternative cerebral metabolic substrates to support brain function during pathological processes is gradually expanding from neurodegenerative diseases to all severities of traumatic brain injury and even spinal cord trauma as well.

## KETONES AS ALTERNATIVE SUBSTRATE EARLY AFTER TRAUMATIC SPINAL CORD INJURY

Ketosis induced by diet or fasting has also been shown to be beneficial after spinal cord injury. Adult male rats given 3:1 ratio ketogenic diet (Bioserv F5848) for 12 weeks starting 4 hrs after cervical injury had decreased spinal lesions, increased expression of GLUT1 and MCT1 vascular transporters and improved forelimb motor function (52). Ketosis induced by every other day fasting for 2-4 weeks improved functional recovery, decreased lesion size and increase corticospinal tract sprouting in adult male rats with thoracic or cervical injury (53, 54). In contrast, every other day fasting in adult mice after thoracic compression failed to show histological or behavioral neuroprotection (55). In the adult mice, the plasma ß-hydroxybutyrate (ßHB) levels did not show significant increases until post-injury day 3, which may have contributed to the lack of neuroprotection. It should also be noted that binge eating in mice is greater than in rats, with mice almost doubling their food intake on the feeding days. This difference in feeding behaviors may also contribute to the different neuroprotective response. This suggests that early alternative substrate intervention is critical in rapidly evolving states of metabolic crisis.

## KETONES AS A CEREBRAL SUBSTRATE DURING LONG-TERM RECOVERY

Recovery from TBI is a dynamic process, with the initial post-injury period occupied by complex ionic and neurochemical pertubations, and later stages of recovery reliant more on the brain's properties of plasticity and reorganization to ameliorate the severity of residual neurologic deficits. Consequently, therapies which prevent maladaptive processes in the immediate aftermath of TBI may in later stages of recovery impair long-term potentiation and learning processes which are necessary for effective rehabilitation. Any putative neuroprotective strategy for TBI must therefore be evaluated in the context of appropriate timing following the injury.

While preclinical studies of ketogenic diet treatment acutely following TBI have demonstrated improved outcome, the optimal timing and duration of post-injury treatment remains unclear. Studies of the ketogenic diet's effects on plasticity and long-term potentiation have been somewhat inconsistent. Although Zhao et al demonstrated impaired visual-spatial memory and reduced brain growth in rats fed a ketogenic diet both with and without prior status epilepticus, this study employed an extremely high fat: carbohydrate + protein ratio of 8.6:1, which is more than two-fold higher than the maximum ratio typically used in clinical practice (56, 57). This extreme diet ratio was associated with lower overall caloric intake, poor weight gain, and inadequate protein consumption to meet growth requirements. This emphasizes the need for body weight controls to be included in experimental designs to monitor response to changes in diet.

Studies addressing the effects of long-term ketone consumption on synapse, axonal sprouting and innervation have not provided consensus on the role of ketone metabolism during long-term TBI recovery. Differential synaptic changes have been observed in senescent rats

after 8 weeks of 10 or 20% medium chain triglyceride diet (Bioserv) (58). In these aged rats, the diet showed opposing morphologic modifications with the stratum moleculare layer of CA1 showing lower synaptic density and fewer synaptic mitochondria, while the outer molecular layer of the dentate gyrus showed greater synaptic density and mitochondrial concentrations. This data brings up an interesting possibility that cellular responses to ketosis may differ regionally and vulnerability associated with aging or trauma may make some cells unable to adapt to different fuel sources (59). Changes in synaptic function as measured by long-term potentiation have also been examined, though inconclusive. The ketogenic diet or calorie restriction for 2-3 weeks in seizure-naïve PND21 rats demonstrated no diet-related impact on short-term plasticity (using paired-pulse modulation) or long-term plasticity (measured through long-term potentiation of the medial perforant pathway) (60). In contrast, PND51-73 rats maintained on the Bioserv ketogenic diet for 3 weeks showed diminished long-term potentiation for at least 48 hrs (61). In normal adult rats, 8 weeks of ketogenic diet did not alter the baseline electrophysiological measures(62). It is unclear based on these two studies whether age alone can account for the differential response.

In addition to direct effects of ketosis on synaptic plasticity, there is evidence that ketosis can affect neurotransmitters and growth factors involved in these processes. Cultured neurons utilizing ßHB have reduced malate-aspartate shuttle activity and diminished glutamate release upon stimulation (63). While decreased excitatory neurotransmission may be desirable for seizure prevention, it could be inhibitory during establishment of new connections during recovery. PND30 rats fed the ketogenic diet for 2 months showed reduced BDNF levels in the striatum but not in the hippocampus (64). BDNF plays an important role in plasticity and recovery after TBI, which may be altered for some cerebral regions after ketosis.

Collectively these effects of ketones provide researchers with insight into the effects of ketosis on brain synaptic function and plasticity, but the mechanisms and how the addition of TBI will complicate these outcomes remain unknown. While research has shown that ketone metabolism is beneficial during the acute phase of TBI, more research is needed to address the cellular changes in gene expression and the role of long-term ketone use after TBI to ensure that the optimal cerebral substrate is available during rehabilitation and recovery.

## OTHER FATTY ACIDS AND TBI

Independent of ketone body action, ω-3 polyunsaturated fatty acids (ω-3 PUFAs) such as docosahexanoic acid (DHA) and eicosapentanoic acid (EPA) have also demonstrated benefit in animal and clinical studies of TBI. α-linolenic acid (ALA) can serve as a precursor to EPA, and subsequently to DHA(65). However the majority of DHA obtained through dietary sources such as fish, seafood and poultry(66–68), as <1% of ALA is converted to DHA in humans. The most prominent ω-3 PUFA in the mammalian brain is DHA, which is highly concentrated in gray matter and due to its flexible structure contributes to the fluidity and function of neural and synaptic membranes (69–72). DHA is essential for normal fetal neurologic development, and has roles in neuronal differentiation, regulating gene expression, learning and memory, and neuronal plasticity(73–77).

In the aftermath of TBI, not only are normal patterns of energy homeostasis disrupted, but factors involved in synaptic transmission, plasticity and learning such as brain derived neurotrophic factor (BDNF) and synapsin I are also decreased. ω-3 PUFA supplementation normalized levels of these depleted neurochemicals, and furthermore improved performance on functional measures of learning and cognition in animal models of TBI(78, 79). Bailes et al.

found that DHA supplementation for 30 days following impact acceleration injury was associated with a dose-dependent decrease in axons positively staining for β-amyloid precursor protein (APP), which is a marker for diffuse axonal injury(80)

Several studies have also examined the potential neuroprotective effects of pre-injury supplementation with ω-3 PUFA. DHA supplementation for 30 days prior to impact acceleration injury was associated with decreased markers of cellular apoptosis and diffuse axonal injury, as well as improved water maze performance(81). Pu and colleagues found that mice pre-treated with ω-3 PUFA including DHA and EPA for 2 months prior to CCI injury had similar cortical lesion volume to those fed a diet inherently poor in ω-3 PUFA, but that hippocampal neuronal loss within the CA-3 region and cognitive/behavior performance were improved. In addition, ω-3 PUFA pre-treatment resulted in white matter preservation through decreased inflammatory response to injury, improved levels of myelin basic protein, more intact myelinated fibers, and improved post-injury conduction velocity of action potentials stimulated across portions of the corpus callosum (82).

## THE USE OF KETONES IN CLINICAL TBI

In spite of the extensive preclinical evidence supporting the neuroprotective benefits of ketones, the ketogenic diet and ω-3 PUFA supplementation, clinical trials are sorely needed to validate the impact of these treatments on global outcome in humans. To our knowledge, only one clinical study has examined the short-term effects of ketogenic therapy in the acute hospital setting. 20 adult patients with severe TBI were randomized to receive either standard enteral feeds or a ketogenic-like diet which was carbohydrate-free with moderately high fat content (83). Those receiving the carbohydrate-free diet demonstrated lower blood lactate concentration,

higher ketone body levels and better urinary nitrogen balance. Long-term follow-up and global outcome measures were not reported. The authors additionally noted that the carbohydrate-free diet was associated with consistent euglycemia, whereas several episodes of hyperglycemia occurred in the group receiving standard nutritional formula. Hyperglycemia has been repeatedly associated with poorer outcome in both pediatric and adult TBI (84–86). It is also important to note that the majority of ketone neuroprotective experimental studies thus far have been conducted in rodents and dose dependent efficacy and therapeutic windows will likely need to be established in each species.

## POTENTIAL PROBLEMS WITH KETONE THERAPY

To translate the extensive experimental data supporting the benefits of ketone metabolism for TBI into clinical practice, an easily implemented method must be identified to safely and quickly increase CSF ketone levels, and induce a shift to cerebral ketone metabolism. In addition, research and development costs must also be taken into consideration, since the safety and efficacy of any novel therapeutic agent must be validated in extensive clinical trials prior to approval for standard clinical use. In contrast, therapies which have already been approved and established can be much more rapidly deployed into clinical use for other indications.

Direct ketone infusion represents one potential therapeutic avenue. In one study using magnetic resonance spectroscopy (MRS) to measure cerebral ketone levels in healthy human adults, intravenous βHB infusion achieving plasma levels of 2.12 mmol/L were associated with approximate cerebral βHB levels of 0.24 mmol/L (87). A separate group testing a novel hypertonic intravenous βHB solution in adult rats achieved cerebral βHB levels up to 0.28 mmol/L (88). In contrast, more substantial increases in CSF βHB levels are achieved by

prolonged fasting. βHB levels of 0.05 mmol/L were detected via MRS in nonfasted adults, increased to 0.60 mmol/L after two days of fasting and 0.98 mmol/L after 3 days of fasting (89). Therefore, intravenous ketone administration may be an inefficient method for inducing changes in cerebral energy metabolism. Strategies designed to primarily increase plasma ketone levels must also target increased ketone transport across the blood brain barrier by monocarboxylate transporters.

Recently, a phase 1 trial tested the pharmacokinetics, safety and tolerability of orally administering a ketone monoester, (R)-3-hydroxybutyl (R)-3-hydroxybutyrate, to healthy adult human volunteers. In the highest dose group of 12 adults drinking a 714 mg/kg ketone monoester solution three times daily, βHB levels averaging 3.30 mmol//L were achieved (90). This approaches therapeutic plasma ketone levels typically achieved during clinical use ketogenic diet for epilepsy (91). However, 12 of 12 subjects who were administered this high dose reported side effects such as nausea, abdominal distention, headache, diarrhea and dizziness. Two individuals were discontinued from the study; one due to severe vomiting and the other due to nausea, diarrhea, chest pain, abdominal distention and upper abdominal pain(90). In light of these significant side effects, this strategy of direct ketone body infusion may also prove problematic due to its effect on insulin/glucagon balance. Both βHB and AcAc infusion in diabetic dogs stimulated pancreatic insulin secretion, which may counteract the ability of glucagon to promote hepatic ketogenesis and maintain the protective ketotic state. (92)

In light of the many regulatory obstacles and clinical trial expenses required to obtain approval for direct oral or intravenous ketone body administration in the clinical setting, acute post-TBI ketogenic diet initiation provides an attractive alternative. In essence, implementation of post-injury ketogenic diet simply involves a straightforward substitution of a ketogenic enteral

formula such as Ketocal (Nutricia North America) or Ross Carbohydrate Free (RCF, Abbott Nutrition) for the standard carbohydrate-based formulas used for tube feeding. Following an initial period of post-injury fasting in anticipation of possible urgent surgical intervention, prompt advancement to full caloric feeds are typically recommended for improved outcome (93, 94). However, in some cases, concurrent injury to the gastrointestinal tract may preclude enteral feeding. Additionally, in clinical practice for the treatment of epilepsy, ketogenic diet implementation requires close monitoring for side effects and complications such as excessive hypoglycemia, excessive acidosis, gastroesophageal reflux, nephrolithiasis, and hypercholesterolemia (95). The ketogenic diet has been urgently initiated in the intensive care unit for refractory status epilepticus in children and adults(96–99). However, the effect of ketogenic diet implementation on TBI-related conditions such as cerebral edema, intracerebral hemorrhage and other systemic injuries must be further evaluated.

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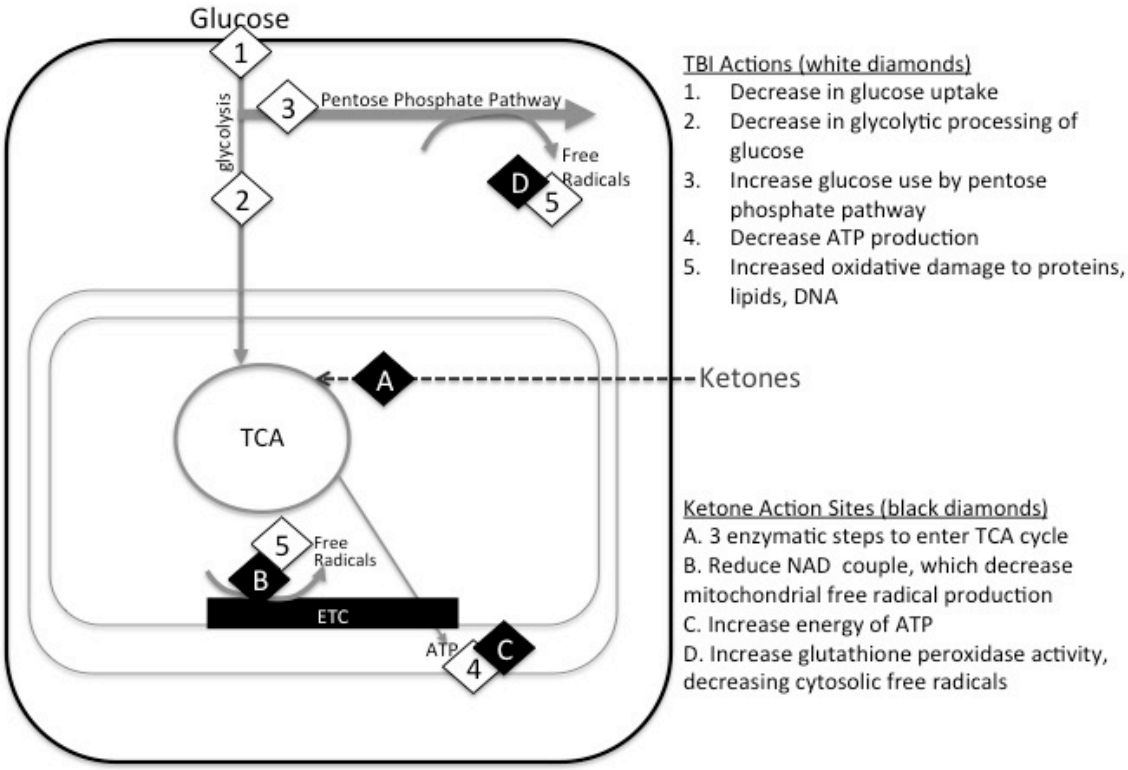


**Figure Legends**

**1) Figure 1: Diagram of the ketogenic sites of action. White diamonds with numbers indicate the metabolic changes that occur after TBI and their consequent changes in energy production and cellular damage. The black diamonds with letters indicate the sites where ketones metabolism can improve cellular energy production and decrease damage.**