

REVIEW ARTICLE

Metabolic Profile and Nutritional Status of Traumatic Brain Injury Patients

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ABSTRACT

The global burden of traumatic brain injury (TBI) is increasing, suggesting that it will become the third leading cause of death and disability worldwide by the year 2020. The brain is known to be the functional regulator for all the metabolic activities inside the body and TBI patients that mostly have a complex metabolic alteration. There are consistent data showing that increased metabolic rate with rapid protein breakdown is common in patients with moderate and severe TBI. The aim of the current scoping review was to summarize the metabolic profile and nutritional status of TBI patients, and to investigate the influence of nutrition therapy on clinical outcomes. A review of the literature published between 2012 and 2017 was conducted. Three databases were searched including PubMed, Google Scholar, and clinical key. Hypermetabolism and malnutrition were known as physiologic consequences of TBI. Pathophysiological mechanisms of malnutrition were multifactorial and related to inadequate nutrient ingestion, abnormalities in the energy expenditure, changes in eating behavior, gastrointestinal disorders, and also side effects of drugs administered. The goal of nutrition therapy is to oppose the hypercatabolism and hypermetabolism. Initiation of nutrition support should begin as soon as the patient has been stabilized and resuscitated.

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Introduction

Traumatic Brain Injury (TBI) refers to any of the following, alone or in combination: brain injury, skull fractures, extraparenchymal hemorrhage -epidural, subdural, subarachnoid- or hemorrhage into the brain tissue itself, including intraparenchymal or intraventricular hemorrhage. Brain injury can be categorized as three types of concussion, contusion, and diffuse axonal injury (1). TBI is typically classified as mild, moderate, or severe based primarily on the duration of

altered mental status (including the degree of responsiveness, as measured by the Glasgow Coma Scale [GCS], and the duration of disrupted memory). These terms can be misleading as they reflect the degree of damage the brain has sustained; they do not necessarily reflect the severity of the disruption in the patient's daily functioning. Individuals with a severe injury can make essentially full recovery, while others with mild-to-moderate injuries can remain significantly disabled for many years (2).

Recent CDC (Centers for Disease Control and

Prevention) data have shown that the total number of TBIs has been increased by 58% over the past 10 years (3). Also, the global burden of TBI is increasing, suggesting that it will become the third leading cause of death and disability worldwide by the year 2020 (4). The annual incidence is estimated to be 200 per 100,000 people, with a peak frequency between 15 and 24 years of age (1). TBI can cause a wide variety of short or long term consequences affecting cognitive function, sensation, motor function, and emotion, depending on its severity. Hallmark symptoms of mild TBI include confusion, lightheadedness, headache, tinnitus, dizziness, blurred vision, fatigue and difficulty with memory, concentration, or attention. Individuals with a moderate or severe TBI often exhibit similar but, more severe symptoms. They also may have seizures, sleep disorders, recurrent nausea and vomiting, impaired speech, ataxia, agitation, depression, anxiety, aggression, and restlessness (5).

The brain is known to be the functional regulator for all the metabolic activities inside the body and TBI patients mostly have a complex metabolic alterations including aberrant cellular metabolism, abnormal metabolic processes, changes in hormone

functions and inflammatory cascade. There are consistent data showing that increased metabolic rate with rapid protein breakdown is common in patients with moderate and severe TBI (6). The aim of the current scoping review was to summarize the metabolic profile and nutritional status of TBI patients, and to investigate the influence of nutrition therapy on clinical outcomes.

Materials and Methods

A review of the literature published between 2012 and 2017 was conducted. Three databases were searched including PubMed, Google Scholar, and clinical key. The screening for relevancy left 19 eligible articles. These were retrieved in full text and reviewed with regard to the following criteria:

The majority of the study patients had a severe TBI (GCS: 3-8) and no patients had a mild TBI (GCS: 14-15), (ii) Related studies to metabolic alterations or nutritional status of TBI patients and (iii) Complete study report available (not only an abstract). We excluded case reports studies, unpublished data or congress presentations/abstracts, and experimental studies. The literature search was completed using the following strategy (Figure 1).

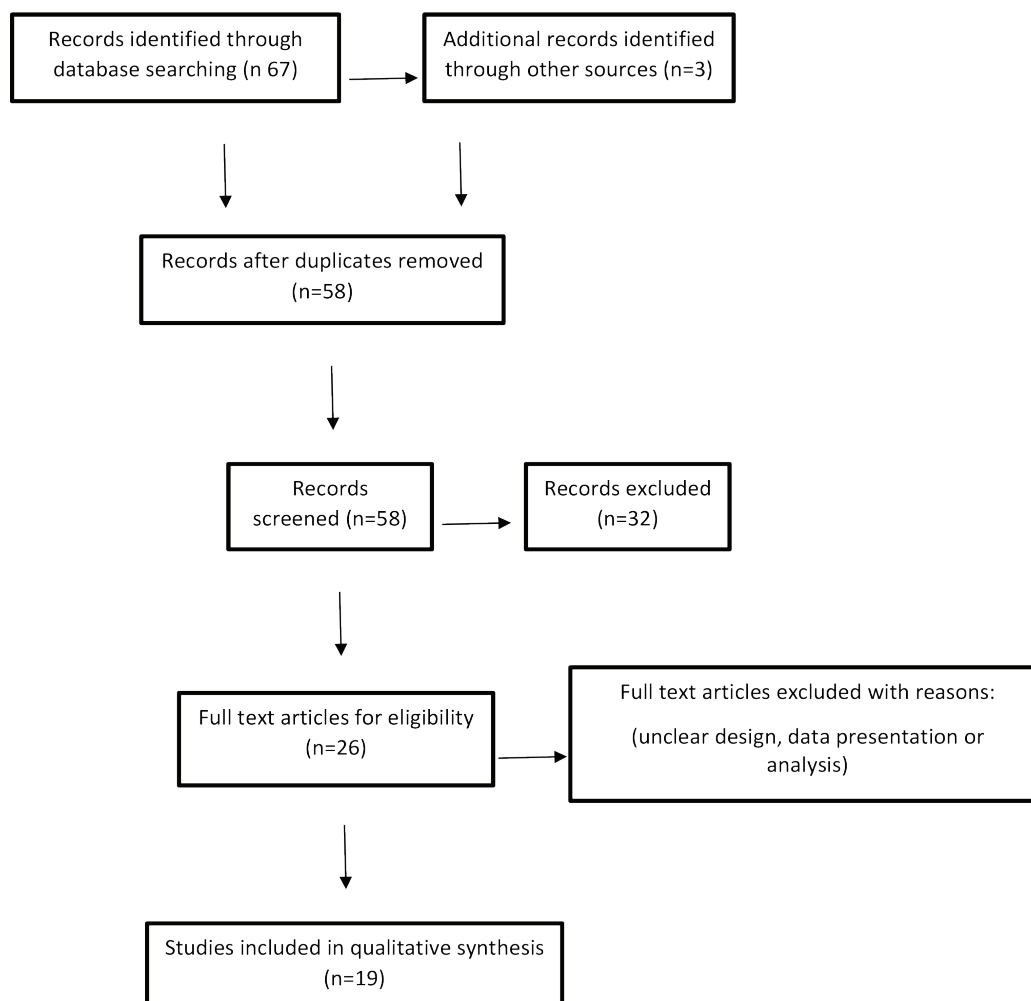


Figure 1: The literature complete search undertaken in the study.

Results

Metabolic Consequences of TBI

The body's response to stress from TBI resulted in production of cytokines (IL-1, IL-6, IL-8 and TNF) and inflammation that led to muscle breakdown, altered amino acids metabolism, and production of hepatic acute phase reactants (7). Head Trauma triggered hypermetabolic and catabolic states, and severely impairing nitrogen homeostasis. It was characterized by disproportional pro-inflammatory cytokine production and release that was associated with increased counter-regulatory hormones (e.g., cortisol, glucagon and catecholamines) release. This process led to increased systemic and cerebral energy needs, even in paralyzed patients. The increased energy needs could persist for long periods (7).

Head injury induced a hypermetabolic state that contributed to increased energy expenditure up to 200% usual values (8). The length of time that metabolic processes remained elevated was reported to last between 20 days and 1 year after injury. Hypermetabolism was followed by hypercatabolism with initial loss of up to 1000 gr/d of muscle tissue and urinary nitrogen excretion rates of 25-30 g/d. Increasing the catabolic rate resulted in increasing the mobilization of amino acids from skeletal muscle which was known as gluconeogenesis, increased nitrogen excretion with accelerated muscle wasting (9). As a consequence of hypercatabolism/metabolism state, many changes were noticed including hyperglycemia, increased loss of lean body mass and increased CRP. Urinary zinc loss also increased that led to depressed serum zinc (6, 10).

Nutritional Status of TBI Patients and Factors Predisposing to Malnutrition

Hypermetabolism and malnutrition were appreciated physiologic consequences of TBI. A systematic review found that moderate or severe TBI was associated with hypermetabolic states up to 200% above normal values. Hypercatabolism was manifested by protein degradation, evidenced by profound urinary urea nitrogen excretion. Nitrogen catabolism in a fasting normal human was only 3 to 5 g/d of nitrogen, whereas nitrogen excretion was 14 to 25 g/d of nitrogen in the fasting patient with severe head injury (1).

The hypermetabolic response was characterized by protein catabolism and altered gluconeogenesis, weight loss, and disruption of mitochondrial function in the brain and systemic tissues. Subsequently, increased energy expenditure had significant impact on substrate utilization and led to a malnourished state (11). Catabolism was further increased by coexistence of injuries from other systems, such

as multiple organ trauma, soft tissue injuries, brain injury, spinal cord injury, maxillofacial injuries, fractures, etc (12). In the absence of nutritional intake, this degree of nitrogen loss resulted in a 10% decrease in lean mass within 7 days. A 30% weight loss increased mortality rate. Replacement of 100% to 140% resting metabolism expenditure with 15% to 20% nitrogen calories reduced nitrogen loss (1). It has been shown that every 10 Kcal/kg decrease in energy intake, increased mortality by 30–40% (13) (Table 1).

Concurrently, patients with moderate to severe brain injury were often unable to meet the increased nutritional requirements because of decreased cognitive and physical function, for example, feeding intolerance, dysphagia, and attention deficits (9). Pathophysiological mechanisms of malnutrition in neurological and neurosurgical disabilities were multifactorial (12). Basilar skull fractures might precipitate injuries to cranial nerves, which were essential for chewing, swallowing, taste, and smell. In addition, they might have many multi injuries and complications including neurologic injury, facial fractures and dental fractures that may delay initiation of an oral diet (1).

Difficulties in chewing food could occur in certain situations, including malpositioned dentures, missing teeth, poor oral hygiene, and oral infections (12). Neurological diseases could cause sensory problems in the mouth or in the throat leading to dysphagia. Some neurological disorders could cause the weakening of certain muscles or muscle groups, making food stuck in the throat while other lead to reduced laryngeal closure, so that (silent) aspiration could result. The coordination of the swallowing process could be affected by certain neurological disorders that adversely affect the motor sequence of swallowing (12).

During aging with a disability, other complications were added in the physiopathological context of "malnourished disabled subjects": pneumonia, aspiration, skin ulcers and neurogenic bowel (i.e. delayed gastric emptying or decreased lower esophageal sphincter pressure) were frequent complications of disabled subjects (12). Many constraints such as required treatments (opioids, sedation, vasopressors) or procedures (surgery, imaging exams, etc.) also strongly participated for interrupting enteral nutrition. Recently, one study had shown that enteral nutrition in TBI was stopped in 63% of days in ICU and 58% of days in ward. Most reasons for interruptions were surgery in 30% of cases, intubation in 28% of cases, and radiologic exams in 28% of cases. High gastric residual volume, vomiting and abdominal distension

Table 1: Nutritional status of TBI patients and factors predisposing to malnutrition

Study	Aim	Participants	Results
Baltazar et al. (3) (2015) retrospective medical record review	To examine the association between early markers of malnutrition in TBI and patient outcomes. Samples tested for initial albumin and prealbumin levels were drawn within 24 hours of admission. The ability to correct albumin level was defined as any subsequent albumin level if the initial albumin level was below normal limits (less than 3.5 g/dL).	251 patients with severe TBI (Abbreviated Injury Score [AIS] 3 or greater)	Initial albumin and initial prealbumin levels were higher in survivors. Forty patients, 28 survivors and 12 non-survivors were found to have low initial albumin levels. Low albumin levels were corrected in 12 survivors (42.9%) and four non-survivors (33.3%). Failure to correct albumin level was associated with death before discharge. Failure to correct albumin levels over the course of hospital admission was associated with death before discharge.
Pelizzo et al. (26) (2017)	Anthropometry, body composition, hormonal and nutritional evaluations	44 neurologically impaired pediatric surgical patients	Energy intake was not adequate in 73.8% of the patients; no correlation between energy intake and BMI was noted. Undernutrition was noted in 34.1% of patients. BMI was <-2 SDS in 47.7% of the subjects; in 29.5% of these, BMI was <-3 SDS. A high correlation between BMI and MUAC was observed (P<0.001). A significant correlation between prealbumin levels with energy intake and MUAC was reported. Vitamin D was far from the optimal level (30–50 nmol/L) in almost all the samples (84%); 50% of the subjects show levels of deficiency.
Chapple et al. (22) (2016) observational study	to quantify energy and protein delivery and deficits over the entire hospitalization for critically ill TBI patients.	37 Consecutively admitted adult patients with a moderate to severe TBI (GCS: 3-12)	Over the entire hospitalization patients had a cumulative deficit of 18,242 (16,642) Kcal and 1315 (1028) g protein. Energy and protein intakes were less in ICU than the ward 1798 (800) vs 1980 (915) Kcal/day, (P=0.015); 79 (47) vs 89 (41) g/day protein, (P=0.001). Energy deficits were almost two-fold greater in patients exclusively receiving nutrition orally than tube-fed 806 (616) vs 445 (567) Kcal/day, (P=0.016) while protein deficits were similar 40 (5) vs 37 (6) g/day, (P=0.616). Primary reasons for interruptions to enteral and oral nutrition were fasting for surgery/procedures and patient related reasons, respectively.
Aadal et al. (9) (2015) A descriptive cohort study	To evaluate weight change, malnutrition, and potential associations after severe brain injury	76 patients admitted to an inpatient rehabilitation hospital	Patients had experienced weight loss of 5.59%±5.89% (P<0.001) at admission at the rehabilitation hospital, and patients with TBI had experienced a greater weight loss than patients with stroke (P=0.01). Thirty percent of patients were at high risk for malnutrition, and 52% of these patients received enteral or parenteral nutrition at admission at the rehabilitation hospital. No association was found between risk of malnutrition and severity of injury, complications, functional outcome, or length of stay.

were found in 10 to 20% of cases (8).

Generally, during hospitalization adequate nutrition was intercepted by anorexia, early satiety, dysgeusia, smelling problems, immobility,

depression, and swallowing disorders, i.e. dysphagia or silent aspiration (caused by a cervical spine stabilization vest like Halo type or other restrictive devices, i.e. a tracheotomy tube, and injuries or nerve

palsies and requires parenteral or enteral support, as soon as possible to prevent pressure ulcers) (12). In summary, patients with acute neurological diseases and chronic neurological diseases increased the risk of malnutrition by multiple factors related to nutrient ingestion, abnormalities in the energy expenditure, changes in eating behavior, gastrointestinal changes, and by side effects of drugs administered (14).

Gut Brain Axis in the Control of Food Intake

The central nervous system regulates food intake, homeostasis of glucose and electrolytes, and starts the sensations of hunger and satiety. The hypothalamus and the brain stem are central sites of appetite regulation. Certain gut hormones including ghrelin, neuropeptide YY, pancreatic polypeptide, GLP-1 and oxyntomodulin, play a physiological role in governing satiety through the hypothalamus. The brain stem transfers information from the peripheral nervous system to the mid- and forebrain. It directly connects with the gut by neuronal pathways and regulates mechanical processes involving appetite and food intake such as chewing and swallowing. Satiety signals from the GI tract are relayed to the area post-trauma of the brain's fourth ventricle via the sensory vagus nerves (15).

The brain receives signals from the gastrointestinal tract through sensory nerves and the circulation. GI hormones transfer information to both the hypothalamus and brain stem. Gut hormone receptors are located on neuronal populations within the ARC, which is also partially accessible to circulating appetite modulators due to its incomplete isolation from the blood-brain barrier. Within the ARC, there exists two distinct populations of neurons responsible for appetite regulation; the POMC appetite-inhibiting neurons and the NPY and AgRP appetite stimulating co-expressing neurons (16). Combining functional MRI with hormonal blood analyses have demonstrated a direct link between changes in plasma concentrations in hormones and modifications in brain regions that are part of the neural circuit of appetite (17).

Several neuronal centers of the hypothalamus participate in the control of food intake. The lateral nuclei of the hypothalamus serve as a feeding center, and stimulation of this area causes an animal to eat voraciously (hyperphagia). Conversely, destruction of the lateral hypothalamus causes lack of desire for food and progressive inanition, a condition characterized by marked weight loss, muscle weakness, and decreased metabolism. The paraventricular, dorsomedial, and arcuate nuclei of the hypothalamus also play a major role in regulating food intake. For example, lesions of the

paraventricular nuclei often cause excessive eating, whereas lesions of the dorsomedial nuclei usually depress eating behavior (18).

These findings suggest that the TBI is responsible for changes in weight through the modification of food intake such as hyperphagia and hypophagia, probably as a result of disruption of the appetite control network following the brain injury. Changes in weight and food behavior have been reported after TBI in short studies and various clinical case-reports. Some reports have described hyperphagia and reduction of satiety. Anorexia following TBI has also been reported. A longitudinal study in 39 children with TBI showed that 15% were overweight 1 year after the TBI (19).

In one study, no significant association was found between the type of cerebral injury according to the initial CT scan, and changes in nutritional status and eating behavior at the subacute/chronic stage. However, this is not a surprising finding, as standard CT and/or MRI assessment at the acute stage lack sensitivity to detect diffuse traumatic axonal injury. It was therefore very unlikely that subtle functional or structural lesions involving the hypothalamus, which could explain changes in eating habits, would be detected with these techniques (19).

Adipokines are expressed in the CNS where receptors for these factors are present and regulate numerous physiological functions such as appetite and energy expenditure. The dysregulation of adipokine production or levels has been correlated with several diseases such as neurological diseases (20). For example, Orexin neuron activity is suppressed by TNF. In 44 consecutive TBI patients, CSF orexin levels were abnormally low in 95% of moderately to severely affected individuals 1 to 4 days after trauma, and 6 months later levels were still significantly low in patients. The poor appetite that is a component of sickness behavior and occurs in chronic inflammatory diseases is also consistent with orexin inhibition by TNF (21).

One explanation is that given TBI compromises the integrity of the blood brain barrier, it could result in the changes in gene expression in the contralateral side of the hippocampus by exposing the brain to circulating factors of peripheral origin (20). Leptin plays a key role in regulating energy intake and expenditure, metabolism, and behavior by directly acting on the CNS. Cerebral damage would also induce the expression of this central adipokine genes that might also impact central energy metabolism following TBI (20). Generally, it is well accepted that the brain, notably the hypothalamus and its complex network, plays a crucial role in the regulation of food intake. It can therefore be expected that TBI

will disrupt this regulation by altering the structures involved (19).

Nutritional Support and Clinical Outcomes

Patients with TBI experience considerable energy and protein deficits in the ICU and these are associated with adverse outcomes (22). Regardless the methods used for assessing TBI patients, having adequate intake and medical care can lead to a reduction in hospital costs, numbers of day hospitalized, numbers of hours of mechanical ventilation and in the overall infection rates (6). To prevent secondary complications, systematic enteral or parenteral nutritional support with focus on protein and energy content is recommended to be initiated immediately after the injury (9).

Advanced nutritional planning should be started 24–48 h after TBI. A multicenter cohort study found that patients receiving enteral nutrition within 48 hours of injury had better survival rates and improved GCS scores (23). For example, in a multicenter cohort study, the EN patients had a greater survival rate and GCS score on the 7th day in the ICU, and a better outcome at 1 month post-injury than non-EN patients. This finding demonstrated that EN within 48 h post-injury was associated with better survival, GCS recovery, and outcome among severe TBI patients (24). In another study, longer time to initiation was associated with increased energy and protein deficit (both $p < 0.001$). A greater energy and protein deficit was associated with longer time until discharge alive from ICU and hospital, and time receiving mechanical ventilation (all $p < 0.001$) (8).

Discussion

There were consistent data showing that increased metabolic rate with rapid protein breakdown is common in patients with moderate and severe TBI during the early post-injury period, while data from the later rehabilitation period are scarce. Further studies are needed to evaluate the metabolic profile at the chronic stage. Hypercatabolism is manifested by protein degradation, evidenced by profound urinary urea nitrogen excretion. In the absence of nutritional intake, this degree of nitrogen loss can result in a 10% decrease in lean mass within 7 days. A 30% weight loss increases mortality rate (1).

However, in one study by Mtaweh et al. (2014) to evaluate energy expenditure of children with severe traumatic brain injury, within the first week after injury, indirect calorimetry measurements were performed daily. Measured energy expenditure obtained from indirect calorimetry was compared with predicted resting energy expenditure calculated from Harris-Benedict equation. Overall, measured

energy expenditure/predicted resting energy expenditure averaged $70.2\% \pm 3.8\%$. Furthermore, children with favorable neurologic outcome at 6 months did not differ from children with unfavorable outcome ($76.4\% \pm 6\%$ vs $64.7\% \pm 4.7\%$, $p = 0.13$). Therefore, contrary to previous works that suggested severe pediatric TBI is associated with a hypermetabolic response (measured energy expenditure/predicted resting energy expenditure $> 110\%$), these researchers suggested that contemporary neurocritical care practices may blunt such a response (25).

Understanding the metabolic requirements of patients with severe traumatic brain injury is the first step in development of rational nutritional support goals that might lead to improvements in outcome (25). Pathophysiological mechanisms of malnutrition in neurological and neurosurgical disabilities are multifactorial. Adequate nutrition is intercepted by anorexia, early satiety, dysgeusia, smelling problems, immobility, depression, swallowing disorders, gastrointestinal changes, and changes in eating disorders (12).

After TBI, changes in weight and food behavior have been reported in short studies and various clinical case-reports. Some reports have described hyperphagia and reduction of satiety. Anorexia following TBI has also been reported. Modification of food behavior and thus of weight can be expected to occur after TBI, because the hypothalamus is the main brain center involved in food intake in humans (19). In one study, no significant association was found between the type of cerebral injury according to the initial CT scan, and changes in nutritional status and eating behavior at the subacute/chronic stage. However, this is not a surprising finding, as standard CT and/or MRI assessment at the acute stage lack sensitivity to detect diffuse traumatic axonal injury. It was therefore very unlikely that subtle functional or structural lesions involving the hypothalamus, which could explain changes in eating habits, would be detected with these techniques. Future studies are needed to assess the association between the type of cerebral injury and changes in nutritional status and eating behavior (19).

Conclusion

Hypermetabolism and malnutrition are appreciated physiological consequences of TBI. Pathophysiological mechanisms of malnutrition are multifactorial and related to nutrient ingestion, abnormalities in the energy expenditure, changes in eating behavior, gastrointestinal changes, and by side effects of drugs administered. The goal of nutrition therapy is to oppose the hypercatabolism

and hypermetabolism. Initiation of nutrition support should begin as soon as the patient has been stabilized and resuscitated.

Conflict of Interest

None declared.

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