Learning Objectives

- Know the deleterious consequences of energy and protein deficit;
- Know the most appropriate macronutrients needs: repartition, amount, time, route;
- Know the reasons for undernutrition and the strategies to prevent and treat them: interruptions, gastrointestinal dysfunctions;
- Know the specific indications of micronutrients, vitamins and trace elements diet supplementation.

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Key Messages

- Traumatic brain and spinal cord injuries patients present hypermetabolism characterized by high caloric energy expenditure and protein loss;
- Energy and protein deficits in traumatic brain and spinal cord injuries patients are associated with a poor outcome and a higher mortality rate;
- No formula enables to evaluate accurately energy requirements in traumatic brain and spinal cord injuries patients; indirect calorimetry will be used if possible and if not provide 25 kcal/kg per day with 1.3 to 2g/kg per day of protein during the acute phase;
- Glycemic control will aim to maintain glucose plasma levels below 1.8-2 g/l;
- Early feeding within the first 48 to 72 hours following trauma is recommended once the patient is hemodynamically stable;
- Enteral nutrition (oral or through a nasogastric/jejunal tube) will be preferred to parenteral nutrition when possible;
• Immune modulating formulas (containing arginine, glutamine, omega-3 fatty acids) and vitamins (D) and trace elements (zinc) supplementation is suggested.

1. Introduction

Traumatic brain injury (TBI) are classified into 3 categories depending on their severity: mild for a glasgow coma scale (GCS) of 13-15, moderate for a GCS of 9-12 and severe for a GCS less than 9. TBI are characterized by a high metabolic rate and nitrogen loss which leads to energy and protein loss. These metabolic modifications are all the more important as severity of TBI increased. Undernutrition is associated with an increased mortality rate and poor outcome. Therefore, it is essential to provide the appropriate amount of caloric and protein feeding, as earlier as possible to avoid these deficits. Macronutrients supply must reach 25 kcal/kg of actual body weight per day (or the dose based on indirect calorimetry) associated with a high protein diet (between 1.2 and 2 g/kg per day). An early enteral nutrition must be favoured, but when insufficient or impossible, parenteral nutrition must be prescribed. Supplementation with omega-3 fatty acids, glutamin, vitamin D and zinc might be beneficial in these patients. Insufficient nutrition delivery is very frequent in TBI due to many reasons related to the trauma, associated procedures and treatments. Therefore, delivered nutrition is about 60 to 70% of that prescribed during the first week after trauma. Gastric paresia, frequent interruptions of enteral diet (surgery, radiographic exams, etc) are responsible for undernutrition. At last, there is no real strong evidence for specific recommendations in this sub-group of critically ill patients. Data concerning patients with spinal cord injury are very scarce, but it seems reasonable to extrapolate nutritional strategies of TBI as factors that worsens spinal cord and brain damage are comparable.

2. Energy and Protein Requirements

2.1 Metabolic Rate and Traumatic/Spinal Cord Injuries

The metabolic rate of TBI has been largely evaluated and 2 meta-analysis confirmed that moderate to severe TBI present an increased resting energy expenditure (1, 2). This elevation may vary from 100 to 200% in 2/3 of patients during the first 2 to 4 weeks following trauma. The most recent meta-analysis which includes 24 studies among which 3 are randomized controlled trials, showed that mean energy expenditure was 75 to 200% of the predictive value (1). These modifications may lead to long-term sequelae such as a loss of weight exceeding 30% in 2/3 of patients during the first 2 to 6 months after injury (3). As a consequence, underfeeding related to non covered energy and protein requirements conduct rapidly in the acute phase to deficits (4, 5). In a prospective observational study including 37 moderate to severe TBI, the mean cumulative energy and protein deficits during hospitalisation were 18242 kcal and 1315 g of protein, respectively (5). Such deficits are associated with an increased morbidity, i.e. longer length of mechanical ventilation and length of stay in ICU and hospital, while no relationship with mortality was found (4). Numerous factors contribute to modify the resting energy expenditure in TBI patients: temperature, sedation, paralyzing agents, mechanical ventilation, barbiturates and severity of the trauma. Sedation is responsible for a 10 to 30% reduction in basal energy expenditure (BEE) (1, 6, 7). Most authors consider that TBI's energy expenditure is 1.4 of BEE and 1 of BEE in case of sedation and curarization, respectively. Hyperthermia which is more frequently present in most severe TBI, is also associated with a higher energy expenditure (7). Therefore, large variations in energy expenditure are observed in TBI and the estimation of caloric requirements is difficult. Sunderland et al (8) reported that predictive formulas did not provide accurate evaluation, as estimated were within 75 to 125% of measured energy expenditure values.
2.2 Caloric and Macronutrients Needed
Because all formulas failed to provide an accurate estimation of energy needed in TBI and spinal cord injury, most experts recommend to measure it using indirect calorimetry when possible. If not (which is frequent for practical reasons), they recommend to provide 20 to 25 kcal/kg BW per day during the acute phase and reach 25 to 30 kcal/kg BW per day in the stable phase (1, 9-13). Glucose amounts should be controlled in those patients in order to avoid severe hyperglycemia and hypoglycemia which are both deleterious on brain and spinal cord injury. Excessive hyperglycemia has been largely reported to be associated with a worsen outcome in observational studies performed in TBI (14-18). On the other hand, strict control of hyperglycemia with insulinotherapy was found to be associated with an increase in brain energetic crisis (elevated intracerebral lactate/pyruvate ratio and glutamate) (19). Moreover, this strategy increases the risk of hypoglycemia. Finally, recent randomized controlled trial and meta-analysis showed that glycemic control aiming to maintain glucose plasma level between 1.5 and 2 g/l did not increase mortality rate nor poor outcome while reducing hypoglycemic episodes compared with a "strict glycemic control" (20-22). Therefore, it is now recommended to avoid excessive hyperglycemia, i.e. > 10-11 mmol/l (1.8-2 g/l) and to maintain a moderate "permissive" glycemic control between 8 and 11 mmol/l (1.4-2 g/l) (23). As a consequence, carbohydrate supply as a part of nutrition in TBI should be ≤ 150 g per day.

High protein intake is commonly proposed in TBI. However, the lower limit to recommend remains discussed. Some observational studies designed with an administration of 1 to 2 g/kg BW per day of protein, have shown an association with an improved nitrogen balance and neurological outcome (24-26). On the other hand, randomized trials reported that protein supply above 2 g/kg BW per day (2 to 2.5 g/kg BW per day) induced a higher positive nitrogen balance as compared with 1.5 to 2 g/kg BW per day (27-29). Most experts suggest to administer at least 2 g/kg BW per day and that protein supply must represent 15 to 20% of total caloric intake (4, 11, 30, 31).

Actual body weight must be considered for calculation of caloric and protein requirements. When body mass index exceeds 25 kg/m², consider ideal body weight.

2.3 Prescribed Versus Delivered Nutrition
Many studies have confirmed that only a part of prescribed nutrition (mean of 60-70%) is really delivered in critically ill patients (32, 33). Similar results have been reported in TBI: only 58% and 53% of energy and protein requirements, respectively were delivered (11). Reasons conducting to this inadequation are multiple. Approximately 50% of TBI exhibits intolerance to enteral nutrition. This dysfunction is well known as a major factor that lead to stop or decrease nutrition. Underfeeding and intolerance are favoured by consciousness impairment, mechanical difficulties such as swallowing abnormalities and gastrointestinal dysfunctions, all of them being related to brain injury (34-40). In an observational trial, Kao et al (38) found that gastric emptying half-life was significantly longer in moderate to severe TBI than in control patients (57.2±20.8 vs 29.4±3.7). Such a dysfunction was observed in 80% of TBI and was more frequent in female, elderly and severe TBI. Gastric/intestinal hypo-/akinesia persist usually during the first 7 to 15 days after trauma (2). It has been reported that only 24%, 41% and 20% of TBI received nutrition on day 1, 2 and 3, respectively (4). Moreover, 70% of them received gastrokinetic drugs (mostly metoclopramide): 29% on day 1, 50% on day 2 and 61% on day 5. Metoclopramide seems rather inefficient or less efficient in TBI than in other critically ill patient and should be associated with erythromycin if not contra-indicated (40, 41). Despite these data, recommendations concerning the use of gastro prokinetic drugs in TBI remains controversial: metoclopramide as the first treatment for the ASPEN-SCCM (11) while erythromycin is not recommended by ESPEN (42).

Small bowel feeding have been also proposed in case of gastric and gut abnormal mobility. Graham et al (26) compared early jejunal to delayed gastric nutrition. They found that early jejunal tube feeding allowed a higher daily caloric supply and nitrogen intake. Such a strategy conduct also to reduce bacterial infections and ICU-length of stay. Moreover, jejunal tube was well tolerated. These data have been confirmed in a meta-analysis showing that jejunal tube was associated with a decreased rate in pneumonia as compared...
with a nasogastric tube (RR = 0.41 [0.22-0.76]). However, data failed to show any
difference in mortality rate and neurological outcome, leading most experts to recommend
jejunal feeding only when the technique can be performed easily or in case of persistent
gastric akinesia despite appropriate strategies (42).
Many constraints such as required treatments (opioids, sedation, vasopressors) or
procedures (surgery, imaging exams, etc) also strongly participate for interrupting enteral
nutrition. Recently, Chapple et al (4) have shown that enteral nutrition in TBI was stopped
in 63% of days in ICU and 58% of days in ward. Moreover the length of interruption was
8.8±3.4 hours and 6.4±2.6 hours in ICU and ward, respectively. 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, vomitings and abdominal distension
were found in 10 to 20% of cases. In more than 2/3 of patients, oral nutrition intake was
not possible due to agitation, confusion or refusal from the patient.

3. Timing and Route for Nutrition

3.1 Timing
The benefit of an early nutrition in TBI has been underlined since more than 10 years (26,
43). A retrospective study including 797 severe TBI found that mortality rate was lower in
the subgroup of patients with a high intracranial pressure receiving early nutrition within
the first 5 days than those who did not (43). Such a strategy was independently associated
with a reduction in mortality rate. Reaching early caloric energy requirements was also
associated with a lower mortality rate. Two meta-analysis have confirmed the benefit of
early nutrition in TBI in terms of neurological outcome and mortality (44, 45). Based on 7
trials, Perel et al (44) showed that early nutrition support in TBI was associated with a
reduction of death (RR = 0.67 [0.41-1.07]) and a trend for an improved neurological
outcome. The most recent meta-analysis included 5 randomized controlled and 2
propective observational trials to compare early, i.e; within 72 hours after trauma, versus
delayed nutrition (45). Results indicate a clear significant reduction in mortality rate, in
the risk of poor neurological outcome, and in the number of infectious complications.
However, current data do not allow to determine the most precise appropriate timing to
initiate feeding in TBI and spinal cord injury, which is probably between the first 48 hours
and day 7, but never after (46). Indeed, it has been shown that similarly with all critically
ill patients, TBI exhibit wide variations in the magnitude and time course of nutritional
requirements according to the severity of injury, comorbidities, cotreatments and stability
of the patient (1). Therefore, some authors suggest to begin nutrition very early during
the first 24 hours after trauma, but to administer about 50% of energy expenditure and
increase it progressively (46, 47). North American Society of Nutrition (ASPEN) and Critical
Care (SCCM) recommend that early enteral feeding with high protein polymeric diet must
be initiated in the immediate post-trauma period, i.e. within 24 to 48 hours of injury, once
the patient is hemodynamically stable (11).

3.2 Route
Two meta-analysis failed to demonstrate any difference between the enteral and the
parenteral route of feeding (44, 45). However, considering beneficial effects of enteral
route found in critically ill patients, such as immunologic response, gut integrity, lower
cost, etc, the ASPEN-SCCM suggest to prefer the enteral route of feeding in TBI (11).
Enteral feeding must be gradually increased to reach at least 50% of the caloric and protein
targets at day 3 to 5. If these objectives are not reached, supplemental parenteral nutrition
must be initiated at day 3 to 5, and in all cases before day 7. When enteral nutrition is
totally contra-indicated, total parenteral nutrition is required in the same delay.

4. Place of the Immunomodulating Nutrition
Immunomodulation concerns essentially 4 nutrients: omega-3 (n-3 polyunsaturated fatty
acids), glutamine, antioxidants (especially vitamin D) and trace elements (especially zinc).
4.1 Polyunsaturated Fatty Acids (PUFAs)
These nutrients are implicated in various cell function and structures, especially in brain: neuronal cell fluidity, neuroplasticity, neurogenesis, neuroinflammation, etc (46). Both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are predominantly present in brain. Promising experimental data showed that DHA and EPA supplementation in TBI conduct to pleiotropic neuroprotective effects such as a reduction in inflammation, apoptosis, excitotoxicity, oxidative stress, an improvement in cell energy and calcium homeostasis in injured axons (48-50). Two observational studies (51, 52) and 1 randomized clinical trial (53) have reported that PUFAs supplemented diet was associated with a reduction in the recurrence or in the risk of ischemic stroke in patients at risk. EPA dietary supplementation demonstrated a decrease in symptomatic vasospasm an mortality in patients with sub-arachnoid hemorrhage (54). In summary, despite abundant laboratory evidence, the role of DHA and EPA dietary supplementation in patient with neurological injuries is not proven.

On the other hand, due to their antithrombotic effects, PUFAs enable to increase the risk of hemorrhage, especially when using high dose (> 6 g per day) (55). As a consequence, until real proofs of their beneficial effects, omega-3 fatty acids dietary supplementation must avoid high dose and it has been suggest to administer moderate doses of 2 to 3 g per day in the setting of TBI (56, 57). Only experimental data reported that EPA infusion 30 minutes after a spinal cord compression decreased tissue injury and improved functional recovery (58, 59).

4.2 Glutamine
Glutamine is a non essential aminoacid which has shown numerous experimental beneficial effects on gut function. The administration of glutamine-enriched enteral diets, either individually (60), or associated with probiotics (61) or with alanine (62) reduced in-hospital length of stay and infections in moderate to severe TBI. But, excessive dose or supplementation in patients with normal glutamine plasma levels, seems to cause harm (63). Therefore, glutamine might be administered in TBI and if prescribed, the appropriate dose must be between 0.3 to 0.5 g.kg BW per day (i.e. 25-50 g per day) during enteral and parenteral nutrition for 7 to 15 days (64, 65).

4.3 Vitamin and Trace Elements
Both vitamin D and zinc have been essentially studied. Zinc (Zn) is a trace element with numerous regulatory roles in neurobiology. Zn deficiency (or excess) contributes to worsen behavior, central nervous system development and neurologic diseases. Zn seems to be implicated in many brain functions and structures, similarly with PUFAs (46, 66). Due to an increased Zn urinary excretion and a reduced bioavailability, TBI is at high risk of prolonged low Zn plasma levels for at least 4 weeks (66-68). Zn intravenous (iv) supplementation for 2 to 4 weeks in TBI was found to improve neurologic outcome and visceral protein amounts as compared with controlled TBI (69). Zn is characterized by a dual neuroprotective (in case of deficit) and neurotoxic (in case of excess) effects. The exact mechanism by which Zn provides its neuroprotective or neurotoxic effect remains unclear (66). There is no strong evidence for Zn supplementation and available data only suggest that in the 2 to 3 weeks following moderate to severe TBI, Zn deficiency might be prevented by a parenteral supplementation of 12 mg Zn-sulphated. After day 15, an oral dose of 22 mg per day could be prolonged. At last there is no data comparing enteral and parenteral Zn administration and no data concerning mild to moderate TBI.

Vitamin D is a fat soluble vitamin which plays a crucial role for maintaining a normal calcium metabolism. Experimental data suggest that vitamin D supplementation, alone or with progesterone, improved neurological diseases, reduced neurological inflammation damage and behavioral impairment (70-72). Schnieders et al (73) reported that TBI were vitamin D deficient. Therefore, some authors suggest to provide vitamin D in association or not with progesterone in TBI (11, 46, 74). However, there is still no real clinical data concerning the potential beneficial effects of vitamin D in patients with a TBI (75).
5. Conclusion and Recommendations

Most of recommendations concerning the nutritional strategy of critically ill patients are available for patients with moderate to severe TBI and spinal cord injury (11, 12, 42). Some specific nutritional abnormalities led recently to elaborate some special guidelines and recommendations dedicated to TBI. Because of a comparable pathophysiology, recommendations for TBI may be extrapolated to spinal cord injury.

1. We suggest that, similar to other other critically ill patients, early enteral feeding with a high protein polymeric diet be initiated in the immediate post-trauma period (within 24 to 48 hours of injury), once the patient is hemodynamically stable (11).

2. Based on expert consensus, we suggest the use of either arginine-containing-immune modulating formulations or EPA/DHA supplement with standard enteral formula in patient with TBI (11). There is no recommendation concerning supplementation with antioxidant vitamins and trace elements in TBI. However, a strategy including additional supply of major vitamins and trace elements might be beneficial (12). Such a mixture has been recently found to improve synapse formation and function in experimental spinal cord injury.

At last, the implementation of a formalized protocol of nutrition in these patients including caloric/protein requirements, procedures enable to improve nutrition delivery (management of gastrointestinal dysfunction), dietician involvement, etc, allows to reduce energy and protein deficit and might reduce mortality rate of TBI (4).
6. References


72. Cekic M, Sayeed I, Stein DG. Combination treatment with progesterone and vitamin D hormone may be more effective than monotherapy for nervous system injury and disease. Front Neuroendocrinol 2009;30:158-72.