REVIEW — DOI 10.51821/86.2.11430

Nutritional status in hepatic encephalopathy and transjugular intrahepatic portosystemic shunt – TIPS, and strategies to improve the outcomes

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Abstract

Hepatic encephalopathy (HE) is one of the most severe complications following transjugular intrahepatic portosystemic shunt (TIPS). The identification and treatment of risk factors associated with the development of this complication may reduce the incidence and severity of post-TIPS HE. Several studies have demonstrated that the nutritional status plays a major role in the outcome of the cirrhotic population, particularly those who are decompensated. Although scarce, there are also studies highlighting an association between poor nutritional status, sarcopenia, fragile status, and post-TIPS HE. If these data are confirmed, nutritional support could become a means for decreasing this complication, thereby enhancing the use of TIPs in the treatment of refractory ascites or variceal bleeding. In this review, we will discuss the pathogenesis of HE, the data that supports an association with sarcopenia, nutritional status and frailty and the implications that these conditions have on the use of TIPS in clinical practice. (Acta gastroenterol. belg., **2023,** 86, **318-322**).

Keywords: cirrhosis, encephalopathy, transjugular intrahepatic portosystemic shunt, sarcopenia, nutrition, frailty.

Hepatic encephalopathy (HE) or portosystemic encephalopathy is defined as a spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with advanced liver disease; it is caused by liver insufficiency and/or portosystemic shunting. Although several determinants may play a role, ammonia is likely to be one of the major contributors to HE. Following its production from diet proteins by gut bacteria, urea is catabolized into ammonia, which in normal circumstances is metabolized by the liver and mostly cleared by kidneys, and to a lesser extent by muscles (1-3).

In patients with cirrhosis and particularly if portal hypertension is present, liver metabolism is impaired and direct shunting of ammonia via portosystemic collaterals takes place; ammonia thus reaches and crosses the blood-brain barrier leading to cerebral dysfunction via different pathways (1-3).

Hepatic encephalopathy is one of the most debilitating complications of chronic liver disease. It severely affects the quality of life of patients and their relatives and thereby has a substantial economic burden on the healthcare system. More importantly, it is associated with decreased survival independently of the model for end-stage liver disease-MELD score and with worse post-transplant outcomes.

According to the West Haven Criteria, hepatic encephalopathy is classified into 5 categories, minimal and grade 1-4. Minimal hepatic encephalopathy (MHE) is characterized by the lack of obvious clinical changes in personality or behaviour, but the presence of minimal neuropsychological changes detectable only via psychometric or neuropsychological tests. Minimal and grade 1 hepatic encephalopathy are referred to as covert encephalopathy and grade 2-4 as overt. The latter can complicate up to 50% of cirrhotic patients, while MHE has been reported in up to 60% of the cirrhotic population. Main risk factors associated with development of overt hepatic encephalopathy (OHE) include prior episodes of encephalopathy, impaired liver function, diuretic use, infections, advanced age, and hyponatremia. Higher rates have been described in patients with higher Child-Pugh or MELD scores (1-3).

Hepatic encephalopathy and transjugular intrahepatic portosystemic shunt-TIPS

Hepatic encephalopathy is one of the most feared complications related to the insertion of TIPS, and together with ischemic hepatitis and cardiac problems, a major factor that deters us from using TIPS more frequently. Indeed, TIPS is an effective therapy of complications of portal hypertension, mainly variceal rebleeding, variceal bleeding in high-risk patients and refractory ascites. OHE has been described in about 20 to 30% of patients undergoing TIPS, with a lower frequency when using smaller covered stents. Like in patients instead of patient without TIPS, major risk factors associated with post-TIPS encephalopathy include prior history of OHE and impaired liver function [higher Child-Pugh and MELD scores, lower albumin levels, arterial hypotension, hyponatremia], advanced age and renal dysfunction. In addition, portosystemic pressure gradient (PSG) lower than 5 mm Hg following the insertion of TIPS is also considered a risk factor. This large decrease in portal

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Submission date: 26/12/2022
Acceptance date: 18/03/2023

pressure is more common with larger stents or VIATORR stents without controlled expansion (4-8).

Functional status and nutrition. Association with hepatic encephalopathy

Nutrition and overall functional status are considered major determinants of outcome in several chronic conditions as well as with aging. In the liver setting, malnutrition, sarcopenia, and frailty are conditions that are frequently reported in advanced stages of liver disease, and that have been shown to negatively impact outcome (3,9-13). Indeed, substantial protein-calorie malnutrition occurs in up to 90% of cirrhotic patients, especially once signs and symptoms of HE have occurred. Even in those with Child-Pugh class A, protein-calorie malnutrition may exist in up to a quarter of cases. There are several reasons behind the typical malnutrition seen in the cirrhotic population including decreased food intake (anorexia, abnormal taste, and poor dentition), maldigestion or malabsorption (decreased bile salt pool, portal venous congestion, bacterial overgrowth) and metabolic changes involving constant consumption of muscle proteins as the energy source (14).

In turn, sarcopenia is strongly linked with malnutrition because of protein catabolism, with increased protein degradation and reduced protein synthesis. Because muscles are relevant for ammonia removal, increased levels of ammonia are more frequently found in sarcopenic cirrhotic patients, which in turn exacerbate hepatic encephalopathy. Myostatin activation in the context of hormonal changes typical of the cirrhotic population (increased TNF-alfa, decreased testosterone and growth hormone) further increases muscle catabolism and muscle loss of function, worsening the vicious circle whereby advanced cirrhosis ± portal hypertension results in malnutrition-sarcopenia which exacerbates hepatic encephalopathy, which in turn leads to further malnutrition/sarcopenia (11,12,15).

In essence, the inadequate metabolism of ammonia by the injured liver results in increased ammonia levels leading to HE, which together with other factors, results in reduced activity, reduced oral intake and increased catabolism leading, in turn, to sarcopenia and frailty with a reduction of muscle mass and subsequent impaired removal of ammonia by skeletal mass, worsening the situation in a vicious circle (3,11,12).

Nutrition status, sarcopenia, frailty, and development of hepatic encephalopathy in the cirrhotic patient with or without TIPS

There are many studies that have evaluated the association between nutrition status, sarcopenia, frailty, and development of HE in the cirrhotic patient with or without TIPS (16-27) (table 1). In a small study including 84 cirrhotic patients, a reduction in handgrip strength, utilized for the assessment of muscle function was found to be an independent predictor of complications, including HE (16). In a second prospective study based on 300 hospitalized cirrhotic patients, muscle depletion evaluated by anthropometry, and impaired muscle function assessed by handgrip strength, were both independently associated with OHE at admission (17). In a third study on 128 unselected cirrhotic patients, cognitive alterations were more frequently detected in patients with malnutrition, and a multivariate analysis showed that the time needed to perform number connection test A was independently correlated to age, Child–Pugh class, malnutrition, and diabetes (18). A study including a cohort of 120 Japanese cirrhotic patients found that the prevalence of MHE was higher in patients with sarcopenia than in those without and sarcopenia was shown to be an independent predictor of MHE at multivariate analysis (19). Another small study found that lower values of adductor pollicis muscle thickness and handgrip strength both correlated with the presence of HE in cirrhotic patients (20). In a study using the Controlling Nutritional Status (CONUT) score (based on albumin, total cholesterol, and total peripheral lymphocyte count) (21), a score originally designed to assess perioperative nutritional and immunological risk in patients undergoing gastrointestinal surgery, the authors demonstrated an association between nutritional status and development of OHE following the placement of a TIPS. In this series, 77 cirrhotic patients undergoing TIPS between 2017 and 2018 were included (mean MELD: 13.5 ± 3.6; Child-Pugh 8.0 ± 1.0). Eleven participants had a history of OHE before TIPS. The mean CONUT score was 6.0 ± 2.3. About half of patients (n=41, 53.2%) experienced OHE events, and a CONUT≥ 5 had a 7.3-fold increased odds ratio (OR) of experiencing this complication following TIPS. In the largest study including 675 patients with cirrhosis evaluated for liver transplantation (LT), myosteatosis was observed in 348 patients (52%) and sarcopenia in 242 (36%), and both were associated with a higher risk of HE, independent of the MELD score (26).

Thus many, yet not all studies (22-24) have demonstrated a positive association between malnutrition and/or sarcopenia and hepatic encephalopathy. Controversial results are likely explained by small sample size of most studies, lack of clear information on the definition of hepatic encephalopathy and time point to assess it, different methodologies to determine the presence and severity of sarcopenia, malnutrition and/or frailty and heterogeneity of studied populations with varying degrees of liver insufficiency and/or portal hypertension. Importantly, the interaction between muscle and cognitive alterations in cirrhotic patients has also been confirmed in patients with TIPS. In one prospective study based on 46 consecutive cirrhotic patients (MELD: 11.3±3.3; Child-Pugh score:7.6±1.5), muscle wasting in cirrhotic patients constituted a strong and independent risk factor for the occurrence of HE after the insertion of TIPS (25). In this series, all patients developing OHE 7+/-9 months post-TIPS (n=21, 46%) were sarcopenic

Table 1. — **Association between sarcopenia (± myosteatosis) and hepatic encephalopathy in cirrhosis**

	Number of cirrhotic patients	Type of study	Tools to determine muscle mass ± function	Type of complication	Association in Univariate analysis with HE	Association in multivariate
Kalaitzakis 2007	128	Prospective	Anthropometry & weight change	OHE & MHE (West-Haven criteria,psycho-metric tests, ammonium)	Yes	Yes
Sörös 2008	223 (NASH)	Retrospective	Anthropometry & bio-impedance analysis	OHE	No	No
Huisman 2011	84	Prospective	Handgrip strength	Cirrhotic complications including OHE	Yes	Yes
Montano-Loza 2012	112 (evaluated for LT)	Prospective	SMI at CT scan	Complications of cirrhosis (including OHE) & mortality	Yes (no association between sarcopenia and HE)	Yes
Merli 2013	300 hospitalized	Prospective	Anthropometry & handgrip strength	OHE and MHE (West-haven criteria, psychometric tests)	Yes	Yes
Mezajunco 2013	116 (cirrhosis + HCC evaluated for LT)	Prospective	SMI at CT scan	Mortality	Yes (no association between sarcopenia and HE)	Yes
Augusti 2016	54	Cross sectional	Anthropometry (adductor pollicis muscle thickness) & handgrip strength	OHE (West-Haven criteria, psychometric tests)	Yes	NA
Hanai 2017	120	Retrospective	Bio-impedance analysis & handgrip strength	MHE (psychometric tests)	Yes	Yes
Nardelli 2017	46 cirrhotic undergoing TIPS	Prospective	SMI at CT scan	OHE post Tips	Yes	Yes
Li 2022	77 cirrhotic undergoing TIPS	Retrospective	Controlling Nutritional Status (CONUT) score	OHE post Tips	Yes	Yes
Bhanji 2018	675 evaluated for LT	Retrospective	SMI at CT scan & muscle attenuation (myosteatosis)	OHE	Yes	Yes
Nardelli 2019	64	Prospective	SMI at CT scan & muscle attenuation (myosteatosis)	MHE & OHE (Psycho-metric tests, West-Haven criteria, ammonium)	Yes	Yes

CT = Computed tomography; HCC = hepatocellular carcinoma; LT = liver transplantation; MHE = minimal hepatic encephalopathy; NASH = non-alcoholic steatohepatitis; OHE = overt hepatic encephalopathy; SMI = skeletal muscle index; TIPS = transjugular intrahepatic portosystemic shunt.

before its insertion while the prevalence of sarcopenia in those without post-TIPS encephalopathy was only 20% (25). Overall, in a recent systematic review with meta-analysis (27) the authors concluded that sarcopenia was associated with HE with an OR of 2.74 (95% CI, 1.87 to 4.01). Interestingly the ORs in the two studies with available data after TIPS seemed higher than those that did not specify their treatments.

Based on these findings, one potential way to reducing the incidence of OHE following the placement of a TIPS could potentially be the amelioration of the nutritional and sarcopenic status of the patient, together with modification of diameter and type of stents. There are several, yet small uncontrolled studies that have shown that this may be a feasible approach (28-32). In a first randomized trial (33), the effect of nutritional therapy was assessed in cirrhotic patients with minimal hepatic encephalopathy. In a tertiary care setting in New Delhi, India, patients with cirrhosis with MHE were assigned randomly to groups given nutritional therapy (30-35 kcal/kg/d, 1.0-1.5 g vegetable protein/kg/d; n =60; age, 42.1 ± 10.3 y; 48 men) or no nutritional therapy (patients continued on their same diet; n=60; age, 42.4 ± 9.6 y; 47 men) for 6 months in 2014. MHE was diagnosed based on their psychometry hepatic encephalopathy score (PHES). Health related quality of life – HRQOL- was assessed by a sickness impact profile (SIP) questionnaire. Primary end points were improvement or worsening in Minimal HE and improvement in HRQOL. There was no significant difference in baseline PHES or SIP scores. After the 6-month study period, a higher proportion of patients in the nutritional therapy group had reversal of MHE (71.1% vs 22.8%; $P < .001$). Patients in the nutritional therapy group also had larger increases in PHES (3.86 ± 3.58 vs 0.52 ± 4.09; $P< .001$) and HRQOL (improvement in SIP score of 3.24 ± 3.63 vs 0.54 ± 3.58; $P < .001$). Overt HE developed in 10% of patients in the nutritional therapy group vs 21.7% of the control group ($P < .04$). Based on this first randomized controlled trial performed in India, the authors concluded that nutritional therapy is effective in the treatment of MHE and is associated with improvement in HRQOL.

In the most recent study, the authors found that the modification of the quantity and quality of the muscle

mass was able to improve the cognitive impairment after TIPS. In this study, the skeletal muscle index (SMI), muscle attenuation (myosteatosis), HE and plasma ammonia were evaluated before and after a mean follow up of 9.8±4 months post-TIPS in 27 cirrhotic patients. The mean SMI & muscle attenuation increased significantly, although not uniformly in all. PHES, ammonia, minimal HE as well as number of episodes of OHE improved significantly in patients with amelioration in SMI>10% despite having similar MELD scores (32).

Conclusions

An association between nutrition, sarcopenia, and HE has been described. Whether muscle function and nutritional approaches, particularly an integrated approach consisting of optimization of the nutritional and dietary regimen, associated with sustainable physical activity will modify the prognosis of patients with minimal hepatic encephalopathy, or that of patients undergoing TIPS placement is still under investigation (34), yet in most centres these approaches are being implemented in the cirrhotic population and are thought to be key elements in the enhanced recovery after surgery, including liver transplantation (35-37) as well as in the cirrhotic population undergoing TIPS placement.

Financial Support

MB received grants from IISCarlos III (INT20/00061, PI19/01360). Ciberehd is partially funded by IISCarlos III.

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