Chapter 16
Branched Chain Amino Acids and Postoperative Quality of Life

Takehiro Okabayashi, Akihito Kozuki, Tatsuaki Sumiyoshi, and Yasuo Shima

Key Points

- Patients with chronic liver disease often reach a state of protein-energy malnutrition, which may influence patient outcomes following surgery and subsequent quality-of-life (QOL).
- Recent assessments of QOL integrate a biochemical health model with a social science model that is based on the patient's subjective perception of functioning and well-being across a range of physical, mental and social aspects of life.
- Since most liver neoplasms occur in patients with chronic liver disease, hepatic resection could potentially reduce QOL in these patients by further compromising liver function.
- Advances in surgical technology and perioperative management have led to hepatic surgical procedures, including liver resection and radiofrequency ablation, being the mainstay of curative treatment for not only hepatocellular carcinoma (HCC), but also metastatic liver tumours.
- Hepatic surgery is still associated with postoperative morbidities due to the inevitable deterioration of liver function following a reduction in functioning liver mass.
- In general, it is recommended that nutrition is individualized according to a patient's nutritional status and monitored to ensure well being and nutritional adequacy.
- Based on the clinical assessment, dieticians should therefore educate patients and carers about sodium and fluid restriction, and appropriate food choices.
- Branched chain amino acid (BCAA) nutritional supplementation improves postoperative QOL over the long term after hepatic resection by restoring and maintaining nutritional status and whole-body kinetics.
- BCAA may also inhibit carcinogenesis in heavier patients with cirrhosis and play a key role in liver regeneration.
- Individualized intervention is thus recommended based on patient's nutritional status.

Keywords Branched chain amino acids • Quality-of-life • Surgery • Liver • Liver cirrhosis • Chronic liver diseases

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Abbreviations

QOL	Quality-of-life
HCC	Hepatocellular carcinoma
BCAA	Branched chain amino acid
PEM	Protein-energy malnutrition
LES	Late-evening snack
GLUT	Glucose transporters
BM	Bone marrow

Introduction

In recent years there has been an increasing coincidence between a patient's point of view and the assessment of their health status. Traditional medical outcomes, which are important endpoints for clinicians, need to be integrated with patients' survival rate after adequate management for various diseases. However, it would be of note that it has been considered patients' opinions on health status, reflecting how they really feel, and how much their disease affects their way of living to be more important, because the treatment consensus over almost all disorders has been established to some extent.

Liver is the central organ for nutrient production and metabolism [1]. Patients with chronic liver disease often become severely malnourished, which can seriously damage their capacity for liver regeneration [2] and increase the risk of hepatocellular carcinoma (HCC). In particular, a state of protein-energy malnutrition (PEM) [3] affects patient outcomes following management as shown by quality-of-life (QOL) estimations [4]. Recent assessments of QOL integrate a biochemical health model with a social science model that is based on the patient's subjective perception of their physical, mental and social functioning and well-being [5].

Recent advances in surgical technology and perioperative management have made hepatic surgical procedures, such as liver resection and radiofrequency ablation, the mainstay of curative treatment for both primary and metastatic liver tumours [6]. However, since most liver neoplasms occur in patients with chronic liver disease, hepatic resection could potentially reduce QOL in these patients by further compromising liver function. Hence, it is important to consider QOL among the more traditional treatment outcomes of operative mortality and long-term survival rates. Some recent studies implicated an important role for nutritional support using branched chain amino acids (BCAA) in the surgical management and postoperative QOL of patients undergoing hepatic resection for liver neoplasms [7, 8]. In this article, we revisit the basic concept of BCAA administration and review how BCAA supplementation affects long-term self-estimated QOL and health in these patients.

Quality-of-Life in Patients with Chronic Liver Diseases

Evaluation of QOL

A QOL assessment concept was developed in the mid-1990s by integrating biochemical and social science models of health assessment [9, 10]. According to the modern concepts of health-related QOL, the principle criteria guiding a patient's acceptance of treatment are often subjective. In patients with hepatobiliary disease, this could include the patients' feelings about their potential QOL following suggested surgical, medical or palliative interventions. Indeed, such perceptions could be more relevant to acceptance of treatment than predicted length of life, because patients are frequently more concerned about quality and disability than about longevity [11]. This is especially true with chronic

Table 16.1 SF-36 and NHP score

SF-36	Physical functioning (PF)	PF scale measures the extent to which physical activities are limited for reasons of health
	Role physical (RP)	RP scale measures how physical health impacts work and daily activities
	Bodily pain (BP)	BP scale measures limitations due to pain
	General health (GH)	GH scale measures how a subject sees personal health and the potential for decline
	Vitality (VT)	VT scale measures how tired/full of energy subject feels
	Social functioning (SF)	SF scale measures how much physical or emotional problems interfere with normal social activities
	Role emotional (RE)	RE scale measures the impact of emotional problems on work and daily activities
	Mental health (MH)	MH scale measures the general state of feeling (e.g. depressed, happy, peaceful)
	Physical Component (Summary) Score (PCS): PCS summarizes the physical health component of SF-36: PF, RP, BP and GH	
	Mental Component (Summary) Score (MCS): MCS summarizes the mental health component of SF-36: VT, SF, RE and MH	
NHP	The Nottingham Health Profile is a multi-dimensional, 45-item questionnaire designed to measure subjective health status. Part 1 comprises six dimensions of health: physical mobility, pain, sleep, energy, social isolation and emotional reactions. Part 2 consists of seven aspects of daily life (i.e. paid employment, jobs around the house, social life, personal relationships, sex life, hobbies and interests and holidays)	

SF-36 short form-36 questionnaires, *NHP* the Nottingham health profile questionnaires

diseases, where survival is not at risk for a long time, and the goal of interventions is to maintain symptom-free and community-living patients.

This conceptualisation is based on the World Health Organization definition of health as “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity”. This definition is so broad that it includes elements that are beyond the traditional domain of medicine and healthcare systems. Opportunity, education, spiritual attitudes, social security, working satisfaction, social relationships and goods availability are elements of QOL that are independent of medicine. Various questionnaires, usually self-administered, have been developed to assess QOL. From the 1990s on, there has been a growing emphasis on assessing QOL in patients with cancer, and this assessment may be as important as the evaluation of long-term survival. The most widely used generic instruments to assess QOL for patients with cancer are the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ)—the EORTC QLQ-C30—and the Functional Assessment of Cancer Therapy—General (FACT-G) [12, 13]. More recently, a study about health-related QOL of chronic liver disease patients with and without hepatocellular carcinoma (HCC) reported that impaired QOL is not associated with the presence of cancer itself, but is dependent on the level of liver function, indicating the importance of preserving liver function [14]. In recent years, the Italian versions of the Medical Outcome Study Short Form-36 (SF-36) and the Nottingham Health Profile (NHP) questionnaires, two generic instruments assessing patients’ well-being, have been validated and used to compare the impacts of chronic diseases in a general population and to determine health policies and resource allocation (Table 16.1) [15].

Poor Health-Related Quality-of-Life of Patients with Cirrhosis

Globally, cirrhosis/chronic liver disease of varying aetiologies is responsible for major mortality and morbidity. Liver cirrhosis is one of the commonest causes of hospitalisation, and a number of studies over the past decade have convincingly demonstrated that health-related QOL is significantly impaired in patients with cirrhosis compared to the general population (Fig. 16.1) [16].

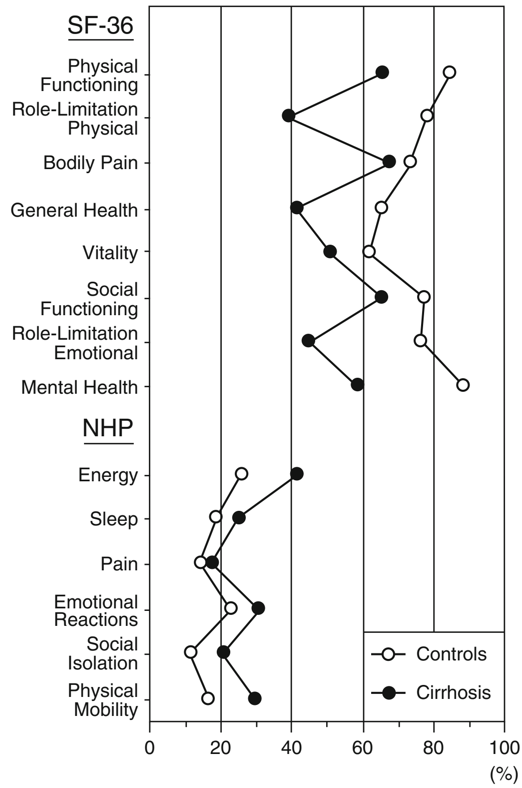

Fig. 16.1 Evaluation of QOL in cirrhosis according to both SF-36 and NHP score [16]. All domains of the SF-36 scored significantly lower in cirrhosis in comparison to normative population [23]

Hepatic Encephalopathy

Hepatic encephalopathy is the occurrence of confusion, an altered level of consciousness and coma as a result of liver failure. In the advanced stages it is called hepatic coma or coma hepaticum. The mildest form of hepatic encephalopathy presents as forgetfulness, mild confusion and irritability, and thus is difficult to diagnose clinically, but it may be demonstrated on neuropsychological testing. The progression of hepatic encephalopathy is characterised by an inverted sleep-wake pattern (sleeping by day, being awake at night), followed by lethargy and personality changes, then by worsened confusion, and finally, a progression to coma [17]. Hepatic encephalopathy thus has a significant impact on the patient's health-related QOL. In addition, minimal hepatic encephalopathy is a part of the spectrum of overt hepatic encephalopathy, with a characteristic cognitive profile that cannot be diagnosed clinically [18]. On follow-up, patients with minimal hepatic encephalopathy are more likely to develop overt hepatic encephalopathy, as compared with cirrhotics without minimal hepatic encephalopathy [19]. Hepatic encephalopathy is associated with poor prognosis and is an independent predictor of survival [20].

Hyperammonaemia

Hyperammonaemia is a condition characterised by raised serum ammonia levels. Mild and transient hyperammonaemia can often be asymptomatic and is usually triggered by protein loads and catabolic states. In symptomatic cases, the clinical features may be variable and episodic. Many cases present with acute mental status changes characterised by confusion, personality changes, irritability, ataxia, visual disturbance, lethargy and somnolence may also report nausea, vomiting and hyperventilation. More severe cases can lead to encephalopathy characterised by stupor and coma. The pathogenesis of hyperammonaemic encephalopathy remains unclear. Changes in mental status have been attributed to high levels of ammonia and the presence of other organic acids, with raised brain ammonia concentrations sometimes present even when the serum ammonia level is normal [21]. Hyperammonaemia can also cause encephalopathy via the inhibition of glutamate uptake by astrocytes [22]. The resulting astroglial processes surround the brain microvessels of the blood–brain barrier and swell in the presence of advanced hepatic encephalopathy. However, despite these significant astroglial changes, the barrier function remains intact, suggesting that cytotoxic rather than vasogenic mechanisms predominate in the pathogenesis of hepatic encephalopathy [23]. As with delirium, elderly patients may present with several concomitant predisposing factors for developing hyperammonaemia and encephalopathy.

Hepatitis Viral Infection and Health-Related QOL

Chronic viral hepatitis infection has been associated with a significant reduction in health-related QOL that is not related to the severity of liver disease. Possible pathophysiological mechanisms affecting QOL in such cases of HCV infection include alterations in mood (increased anxiety and depression) and cognition, together with changes in both the midbrain serotoninergic and striatal dopaminergic systems, irrespective of viraemia or state-ofliver function [24]. The existence of brain alterations directly caused by HCV is evidenced by reported deficits in attention, executive function and verbal learning, by electroencephalogram recordings slowing in the absence of liver cirrhosis and/or substance abuse disorder, and atypical changes on magnetic resonance spectroscopy in HCV-infected patients. It remains controversial whether QOL in patients with HBV-associated cirrhosis is reduced compared to that in patients with HCV-associated or HBV/HDV-associated cirrhosis. Another study showed less impairment of QOL in patients suffering from HBV-associated cirrhosis compared to other causes of cirrhosis such as HCV or cholestasis [25]. However, overall the number of chronic hepatitis B patients reporting reduced QOL compared to patients with hepatitis C was small. Hence, more studies are required to confirm the poor QOL in patients with hepatitis B viral infection.

Serum Sodium and Ascites

A previous study demonstrated the importance of serum sodium concentration for health-related QOL in cirrhosis, whereby patients with hyponatraemia reported a marked impairment in health-related QOL compared to patients with normal serum sodium concentration [26]. Hyponatraemia is common in patients with cirrhosis and ascites and its frequency increases with disease progression [27]. Hyponatraemia with concomitant hypo-osmolality is associated with an adaptive response of the central nervous system aimed at preventing the passage of fluid from the extracellular to the intracellular space and the development of cerebral edema. In patients with marked hyponatraemia, a low-grade cerebral edema exists despite this adaptive brain response and increased ammonia levels also play a role in low-grade cerebral edema [28]. The value of serum sodium concentration in the prediction of health-related QOL persisted after adjustment for possible confounding factors related to the severity of liver failure. Furthermore, serum sodium level was an independent predictive factor in both physical and mental summary scores of health-related QOL, and in six of the eight domains of the SF-36: role physical, physical functioning, general health, social functioning, vitality and mental health [26].

QOL in Patients Undergoing Liver Resection

Branched Chain Amino Acids (BCAA) Improved Both PEM and QOL

Protein-energy malnutrition (PEM) is a common finding in chronic liver disease and affects about 50 % of patients with liver cirrhosis [4]. Since malnutrition adversely affects clinical outcomes, guidelines of the European, American and Japanese Societies for Parenteral and Enteral Nutrition advocated nutritional support for cirrhotic patients [29, 30], recommending the following consensus nutrition standard: 35–40 kcal/kg/day in energy and 1.2–1.5 kcal/kg/day in proteins [29]. However, such standards are not always pertinent and should be altered depending on conditions such as race, intensity of daily activity, PEM, glucose intolerance, protein intolerance and obesity. Flexible handling of the ESPEN guideline is therefore necessary, and calorimetry might be the best way to assess the nutritional status of patients with liver cirrhosis. Possible treatments for PEM include BCAA supplementation and a late-evening snack (LES). BCAA effectively corrects protein malnutrition by increasing plasma albumin, and prolongs event-free survival in patients with advanced cirrhosis [4]. Since energy deficiency is related to worse survival rates, it is also important to address the early-morning energy starvation that is typical in cirrhosis and equivalent to a 3-day starvation period in healthy individuals. To this end, the ESPEN and ASPEN guidelines recommend a LES or divided meals to reduce the starvation period between dinner and breakfast. BCAA as a LES is an ideal supplement in patients with cirrhosis because it provides more energy and protein than the ordinary enteral formula or BCAA granules, significantly reduces fatigue, and improves energy metabolism, protein levels and nitrogen balance [31]. Furthermore, a Hong Kong study also showed that long-term dietary supplementation with BCAA twice daily significantly reduced complications such as ascites and peripheral edema, and improved survival in patients undergoing chemoembolization for HCC [32].

QOL After Curative Hepatectomy

Postoperative QOL

Since most liver neoplasms occur in patients with chronic liver disease, hepatic resection could potentially reduce QOL in these patients by further compromising liver function. QOL assessment has proven to be a valuable parameter for such patients and surgeons and may be helpful in determining the optimal treatment. As an outcome parameter, QOL is considered as important as disease-free and overall survival. In various benign and malignant liver diseases, surgical management is a common procedure with intent-to-cure treatment, as a result of recent advances in surgical technology and perioperative management. Although major and minor liver resections are both safe procedures, little is known about postoperative QOL in these patients [33]. Recent studies indicated that QOL returns to baseline within 3–6 months after liver resection for malignancies in most cases (Fig. 16.2) [34].

BCAA-Enriched Nutritional Support in Surgical Patients (Table 16.2)

In a prospective randomized clinical trial, the San-in Group of Liver Surgery [13] studied the effects of long-term oral administration of BCAA after curative resection of HCC. Between 2 and 3 weeks after surgery, 75 patients were randomized to receive oral BCAAs (Aminoleban EN) at 100 g/day for 1 year, and another 75 patients were assigned to a control group. Flapping tremor was less common, body weight was increased and performance status was better in the BCAA-treated group than in

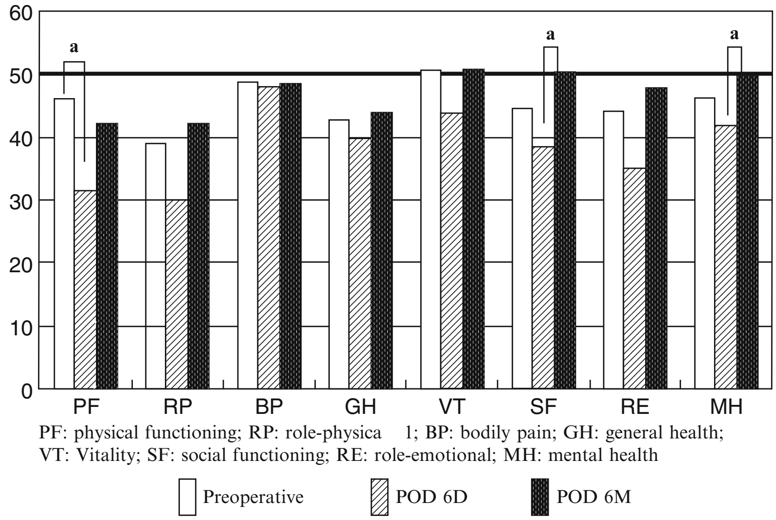

Fig. 16.2 Postoperative QOL after liver surgery ([a]$P<0.05$) [34]. The scores of all eight parameters also decreased immediately after the operation (at POD 6D). However, they recovered at POD 6M to levels comparable to those before the operation [34]

Table 16.2 Effect of BCAA-enriched nutritional support in surgical patients with liver cancer

Author [reference]	Study design	Administration	Benefits of BCAA
San-in group [13]	Prospective 150 patients	Aminoleban EN	• Improved clinical features (body weight) • Improved laboratory data (red blood cell, serum albumin level and Fischer molar ratios)
Meng et al. [8]	Prospective 44 patients	Aminoleban EN	• Shorter postoperative hospital stay • Higher haemoglobin level, higher sodium level, higher albumin level and lower bilirubin during the postoperative course
Togo et al. [36]	Retrospective 43 patients	LIVACT	• Rapid improvement in protein metabolism and inhibition of progression to liver cirrhosis
Okabayashi et al. [34]	Retrospective 36 patients	Aminoleban EN	• Shortened hospitalisation after surgery • Restoration of peripheral lymphocyte count and serum total cholesterol level at 3 months after the operation
Okabayashi et al. [37]	Retrospective 112 patients	Aminoleban EN	• Reduced morbidity associated with postoperative complications • Shortened duration of hospitalisation
Ishikawa [38]	Prospective 24 patients	Aminoleban EN	• Higher serum erythropoietin levels after liver surgery
Okabayashi et al. [35]	Prospective 96 patients	Aminoleban EN	• Significant improvement in QOL after hepatectomy • Restored and maintained nutritional status
Ichikawa et al. [39]	Prospective 56 patients	LIVACT	• Reduced early recurrence after hepatic resection in patients with HCC

controls throughout the 1-year period (Fig. 16.3a). BCAA treatment also significantly increased red blood cell and serum albumin levels in patients with Child grade B and C disease. Substantially similar effects were observed in patients treated with major hepatic resection. The San-in Group summarized that long-term oral nutritional support with BCAAs after resection of HCC is beneficial in

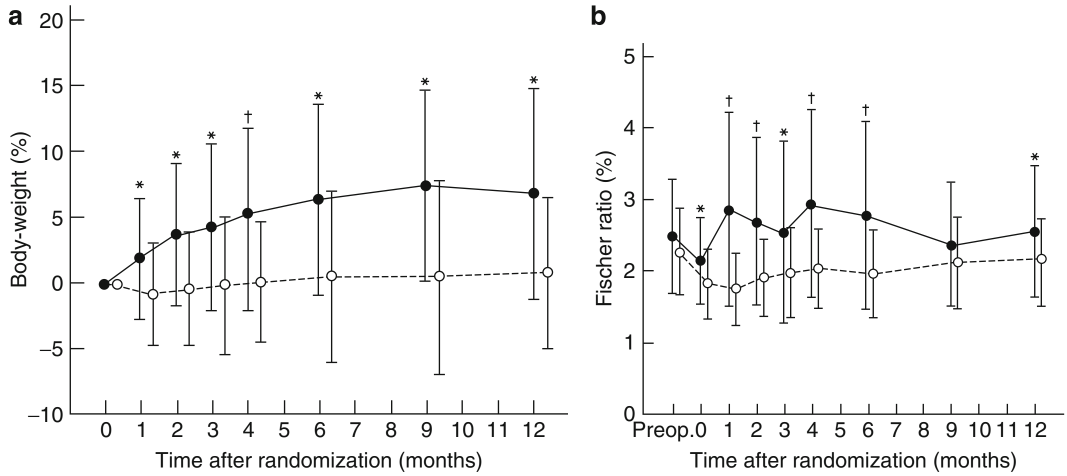

Fig. 16.3 The effect of BCAA [13]. Figure 16.3a, Percentage changes in body-weight in patients treated with BCAA (*black circle*) and controls (*white circle*). Values are mean (standard deviation). *$P<0.01$, †$P<0.001$ versus control group. Figure 16.3b, Changes in Fischer's molar ratio in patients with BCAA (*black circle*) and controls (*white circle*). Values are mean (standard deviation). *$P<0.05$, †$P<0.001$ versus control group [13]

improving clinical features and laboratory data without increasing the rate of tumor recurrence, particularly in patients with advanced cirrhosis or after major hepatic resection (Fig. 16.3b).

In a prospective study, Meng et al. [8] evaluated the effect of BCAA treatment in patients undergoing liver resection for HCC. A prospective randomized controlled clinical trial was conducted involving 44 patients. The BCAA group (21 patients) received Aminoleban EN in addition to a normal diet for 12 weeks and the control group (23 patients) received an isonitrogenous and isocaloric diet only. The BCAA group had a shorter hospital stay, and showed a significantly higher haemoglobin level, higher sodium level, higher albumin level and lower bilirubin level during the postoperative course (Fig. 16.4). The authors concluded that Aminoleban EN is safe to administer and does not have significant adverse effects, while contributing to a shorter hospital stay and quicker improvement of liver function in the early postoperative period (Fig. 16.4).

In a retrospective study involving 43 elective hepatectomized patients, Togo et al. [36] evaluated the usefulness of granular BCAA after hepatectomy for liver cancer complicated with liver cirrhosis. In the BCAA group (21 patients), postoperative ascites and edema tended to improve earlier than in the control group (22 patients), and nutritional status based on serum albumin and total protein levels recovered immediately after liver surgery in the BCAA group. Furthermore, the BCAA group showed a more rapid improvement in hyaluronic acid and type IV collagen 7S levels compared to controls.

In a large retrospective study involving 112 elective hepatectomized patients, Okabayashi et al. [37] evaluated the effects of BCAA-enriched nutrient support for patients undergoing liver resection for HCC. These patients were divided into two groups: 40 patients received perioperative supplementation of a BCAA-enriched nutrient mixture (BCAA group) and 72 patients had no supplement (control group). Laboratory data, postoperative complications, duration of hospitalisation and survival were compared between groups. The overall incidence of postoperative complications was lower in the BCAA group (17.5 %) than in the control group (44.4 %) ($P=0.01$). Among the postoperative complications, surgical site infection and bile leakage were observed in 5 % of patients in the BCAA group and in 15.3 % and 12.5 % of patients in the control group, respectively. Ascites appeared after the surgery in 7.5 % of patients in the BCAA group and in 16.7 % of control patients, while the duration of hospitalisation was significantly shorter in the BCAA group than in the control group ($P<0.05$).

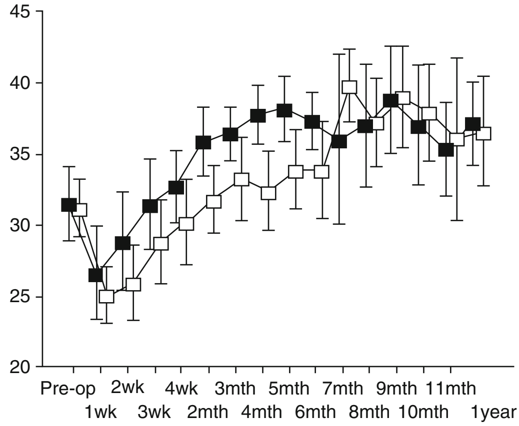

Fig. 16.4 The effect of BCAA on postoperative albumin levels [14]. Mean albumin level (g/dL; 95 % confidence interval). (*Black square*), BCAA group; (*white square*), control group. Albumin level was significantly different in favour of the BCAA group in the postoperative period [14]

The authors suggested that their perioperative BCAA supplementation protocol is clinically beneficial in reducing the morbidity associated with postoperative complications and in shortening the duration of hospitalisation of patients with chronic liver disease who undergo liver resection for HCC.

In a prospective study involving 24 elective hepatectomized patients, including some with a non-hepatitis liver, Ishikawa et al. [38] studied the benefits of perioperative oral nutrition (ON) with BCAA. The patients (20 with malignant liver tumors and 4 with benign liver tumors) were randomly assigned to receive perioperative ON with BCAA (11 patients, BCAA group) or a usual diet (13 patients, control group). The BCAA group received a BCAA supplement twice daily plus a usual diet for 14 days before operation and on days 1–7 after operation. Two of the eleven patients in the BCAA group developed postoperative complications, as compared with 3 of the 13 patients in the control group (18.2 % vs. 23.1 %, $P=0.7686$). Among patients with non-hepatitis, serum erythropoietin (EPO) levels on POD 3, 5 and 7 were significantly higher in the BCAA group than in the control group ($P=0.0174$, $P=0.0141$ and $P=0.0328$, respectively). The short-term ON support with BCAA was thus associated with higher serum EPO levels in patients with non-hepatitis who underwent curative hepatic resection, and higher EPO levels might be beneficial in protecting liver cells from ischemic injury and preventing intraoperative haemorrhage associated with lower perioperative levels of alanine aminotransferase and aspartate aminotransferase in serum.

In a prospective randomized clinical study, Okabayashi et al. [35] assessed the impact of oral supplementation with BCAA-enriched nutrients on postoperative QOL in patients undergoing liver resection. To our knowledge, this was the first prospective clinical study evaluating an association between perioperative supplementation of BCAA and postoperative QOL. Patients were randomly assigned to receive BCAA supplementation (BCAA group, $n=48$) or a conventional diet (control group, $n=48$). Postoperative QOL and short-term outcomes were regularly and continuously evaluated in all patients using a short-form 36 (SF-36) health questionnaire and by measuring various clinical parameters. This study demonstrated a significant improvement in QOL after hepatectomy for liver neoplasm in the BCAA group based on the same patients' preoperative SF-36 scores (Fig. 16.5). Perioperative BCAA supplementation preserved liver function and general patient health in the short term compared to a normal diet. The authors on this study concluded that BCAA supplementation improves postoperative QOL after hepatic resection over the long term by restoring and maintaining nutritional status and whole-body kinetics.

In a prospective randomized clinical study, Ichikawa et al. [39] studied the effect of oral supplementation with BCAA on the development of liver tumorigenesis after hepatic resection in HCC patients. Fifty-six patients were randomly assigned to receive either BCAA supplementation orally for 2 weeks before and 6 months after hepatic resection (BCAA group, $n=26$) or a conventional diet

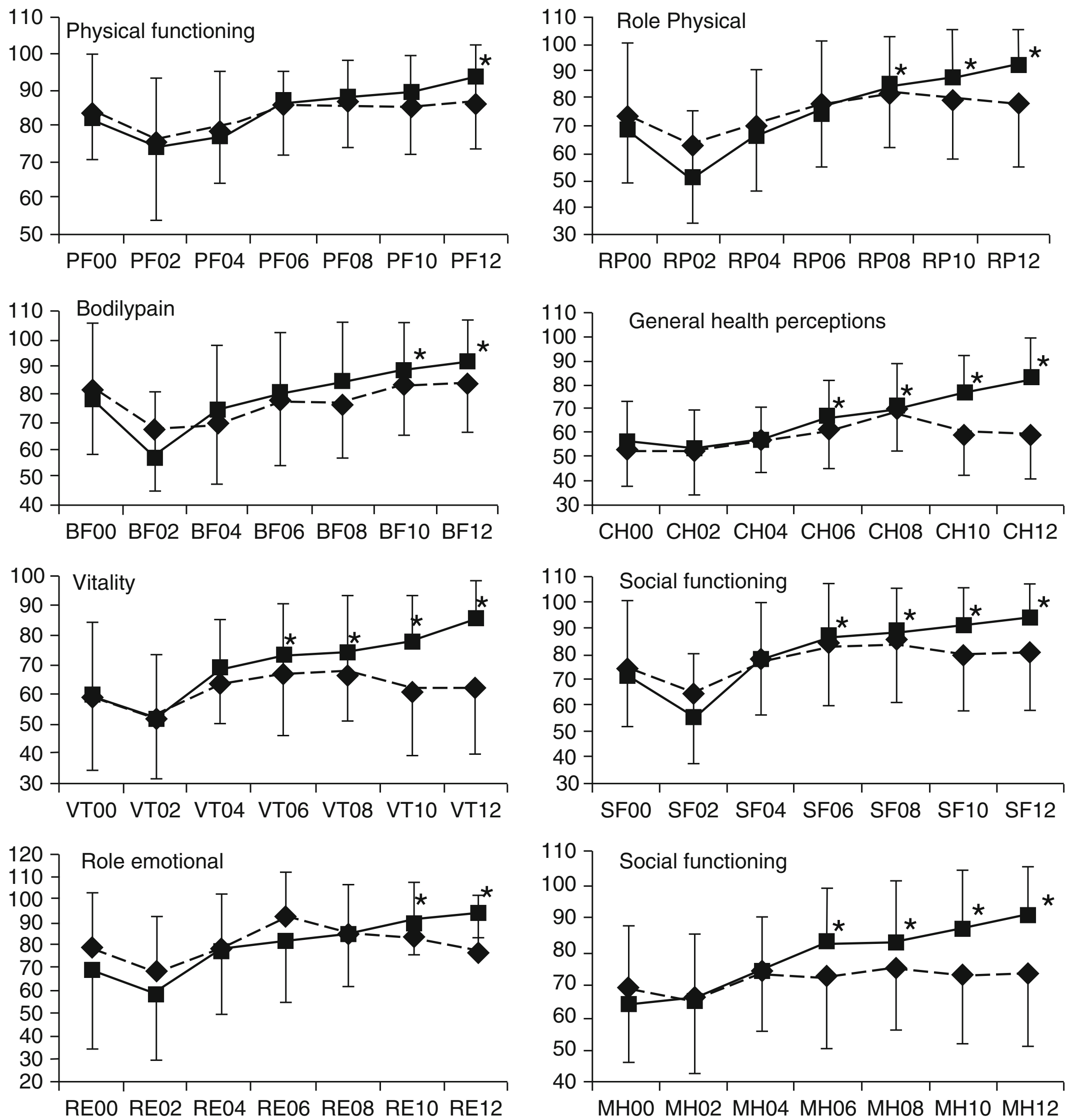

Fig. 16.5 Trends of Norm-based score by SF-36 in the group administered BCAA and the control group [35]. Trends of Norm-based score by SF-36 in the group administered BCAA (*solid line*) and the control group (*broken line*) (*$P<0.05$, compared to preoperative score) [35]. All scores decreased immediately after the operation. However, general health measures including perceptions of health and well-being, vitality, social functioning, and mental health improved by 6 months postoperative to at least preoperative levels in the AEN group [35]

(control group, $n=30$). Postoperative tumor recurrence was continuously evaluated in all patients by measuring various clinical parameters. Recurrence rate at 30 months after surgery was significantly better in the BCAA group than in controls. Interestingly, tumour markers, including AFP and PIVKA-II, significantly decreased at 36 months after liver resection in the BCAA group in comparison to the control group. These findings therefore indicated that oral supplementation of BCAA also reduces the incidence of early recurrence after hepatic resection in patients with HCC, and this treatment regimen offers potential benefits for clinical use in such patients, even in cases with a well-preserved preoperative liver function.

BCAA Improved Perioperative Insulin Resistance

HCV infection causes insulin resistance [40], which is a known risk factor for HCC and reduced long-term survival. Insulin resistance is therefore a potential therapeutic target in patients with HCV infection. BCAA may also play an important role in improving insulin resistance, and in experimental studies using rodents, BCAA induced glucose uptake in skeletal muscle, adipocytes and hepatocytes. Furthermore, in a rat model of liver cirrhosis induced by CCl_4, leucine and isoleucine promoted glucose uptake in skeletal muscle [41]. This effect might occur due to up-regulation of the glucose transporters 4 and 1 (GLUT4 and GLUT1) and/or the rapamycin-dependent activation of glucose synthase in skeletal muscle. Interestingly, a recent human study [42] found that oral supplementation of BCAA for 4 and 6 weeks reduced HOMA-IR in two cases with HCV-related liver disease.

Glucose metabolism is generally adversely affected in patients following major surgery, with hyperglycemia a possible result of postoperative insulin resistance due to reduced glucose uptake by skeletal muscle, adipose tissue and liver [43]. Patients may also develop hyperglycemia due a combination of surgical stress and postoperative insulin resistance. Indeed, insulin resistance after major surgery is well documented and its development is related to the magnitude of surgery [44]. Insulin infusion support to maintain normal glucose levels thus reduces morbidity and mortality rates in critically ill patients, and preoperative management of whole-body insulin resistance is required. Interestingly, preoperative oral administration of carbohydrate reduces postoperative insulin resistance in patients with colorectal resection [43]. Furthermore, short-term infusion of amino acids following colorectal surgery can reduce insulin resistance since endogenous glucose production and glucose clearance is decreased [45]. However, it is uncertain whether preoperative dietary supplementation with carbohydrates and BCAA improves postoperative insulin resistance.

To address this question, Okabayashi et al. [40] conducted a randomized clinical trial in which 26 patients undergoing a hepatectomy for the treatment of a hepatic neoplasm either received a supplement of carbohydrate and BCAA prior to surgery or had no supplement. The postoperative blood glucose level and the total insulin requirement for normoglycemic control during the 16 h following hepatic resection were determined using a closed-loop glycemic control system. Postoperative insulin requirements for normoglycemic control in the group with preoperative nutritional support was significantly lower than that in the control group ($P=0.039$), indicating that preoperative oral administration of carbohydrate and BCAA is clinically beneficial and reduces postoperative insulin resistance in patients undergoing hepatic resection.

Future: Improving Postoperative QOL According to Liver Regeneration Following the Administration of BCAA

Liver failure is a potentially life-threatening condition for which organ transplantation is the only definitive therapy. However, the current shortage of available livers for transplant results in the death of many patients while awaiting transplantation. Thus, it is imperative that new approaches for repairing the liver are developed, so that the need for transplanting a partial or complete human liver to cure the patient can be eliminated. Presently, cell-based therapies represent one of the most promising alternative solutions to entire or partial liver transplantation. Unfortunately, human livers would still be required as a source of cells and the isolation of human hepatocytes remains difficult and inefficient. Furthermore, differentiated hepatocytes cannot yet be effectively expanded in culture, greatly limiting the cell numbers obtained from each liver. Numerous studies have therefore concentrated on culturing and differentiating stem cells from different sources that can be readily isolated using non-invasive procedures, to give rise to hepatocytes both in vitro and in vivo. An added advantage of a stem-cell approach is that many of these cell populations can be expanded significantly in vitro, making it possible to generate large numbers of cells for transplantation from a fairly small initial number. Since some of these stem cell populations are present within the adult, and could thus be isolated from the patient to be treated, the production of personalized, immunologically matched hepatocytes is possible [46].

Liver regeneration is unique among organ systems [47]. In the adult liver, there are two major populations of cells that have been thought to explain liver regeneration and/or repair. The first consists of unipotential cells, specifically hepatocytes and bile duct epithelial cells that regenerate during normal tissue turnover. The second population consists of bipotential cells, intrahepatic liver stem cells and/or oval cells that can differentiate into hepatocytes and bile duct epithelial cells. Recent reports suggest that bone marrow (BM) stem cells may harbor unexpected developmental plasticity [48], although it remains unclear precisely how and to what extent BM cells contribute to liver regeneration, and whether it is by cell fusion, transdifferentiation or both. Previous studies reported that under certain conditions BM cells are recruited into the liver and become not only Kupffer cells, endothelial cells, oval cells, stromal cells and cholangiocytes, but also functioning hepatocytes [48]. Further examination is required to address the possible association between BCAA and liver regeneration, especially the mechanisms by which BM-derived extra-hepatic stem cell develop after liver resection with perioperative BCAA supplementation.

Liver cirrhosis negatively impacts the patient's nutritional status, with derangements in energy expenditure and in protein, carbohydrate and fat metabolism. Common complications of cirrhosis such as ascites, hepatic encephalopathy and esophageal varices require appropriate nutritional intervention. However, for patients with hepatic encephalopathy, the evidence is controversial; while some studies indicate that protein restriction is beneficial, others found that this strategy does not have apparent benefits in acute encephalopathy. For patients unable to tolerate animal proteins, other protein sources should be considered, such as proteins from vegetables or BCAA-enriched formulations [46]. In general, it is recommended that nutrition is individualized according to a patient's nutritional status and monitored to ensure well being and nutritional adequacy. Following the assessment, dieticians should educate patients and carers about sodium and fluid restriction and appropriate food choices. Nutrient-dense meals, snacks and oral supplements are recommended.

Conclusions

Supplementation of BCAA has been shown to improve the nutritional status and QOL in patients with cirrhosis, preventing complications and prolonging survival, including in those patients undergoing chemoembolization and liver resection for HCC. BCAA may also inhibit carcinogenesis in heavier patients with cirrhosis and play a key role in liver regeneration. Individualized intervention is recommended based on each patient's nutritional status.

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