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Branched-chain amino acids as a protein- and energy-source in liver cirrhosis

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Abstract

Protein-energy malnutrition (PEM) is a common manifestation in cirrhotic patients with reported incidences as high as 65–90%. PEM affects largely the patients' quality of life and survival. Thus, diagnosis of and intervention for PEM is important in the clinical management of liver cirrhosis. Supplementation with branched-chain amino acids (BCAA) is indicated to improve protein malnutrition. As an intervention for energy malnutrition, frequent meal or late evening snack has been recently recommended. Plasma amino acid analysis characterizes the patients with liver cirrhosis to have decreased BCAA. Such reduction of BCAA is explained by enhanced consumption of BCAA for ammonia detoxication and for energy generation. Supplementation with BCAA raises in vitro the synthesis and secretion of albumin by cultured rat hepatocytes without affecting albumin mRNA expression. BCAA recover the impaired turnover kinetics of albumin both in rat cirrhotic model and in cirrhotic patients. Longer-term supplementation with BCAA raises plasma albumin, benefits quality of life issues, and finally improves survival in liver cirrhosis. Recent interests focused on the timing of administration of BCAA, since daytime BCAA are usually consumed by energy generation for physical exercise of skeletal muscles. Nocturnal BCAA seem to be more favorable as a source of protein synthesis by giving higher nitrogen balance. This minireview focuses on the basic and clinical aspects of BCAA as a pharmaco-nutritional source to control PEM in liver cirrhosis.

Protein-energy malnutrition (PEM) is a common manifestation in cirrhotic patients with reported incidences as high as 65–90% (Table 1) [1–3]. Protein malnutrition is usually represented by reduced serum albumin level (visceral protein) and by decreased skeletal muscle volume (muscular protein) in cirrhotics. The latter can be measured with conventional anthropometry as arm (or midarm) muscular circumference (AMC). Energy malnutrition is typically observed as an altered profile of thermogenesis such as reduced carbohydrate oxidation, increased fat oxidation, and subsequent decline of non-protein respiratory quotient. PEM affects largely the outcome of the patients by determining both their quality of life and survival (Fig. 1) (for recent studies, see [2] on protein malnutrition and [3] on energy malnutrition). Long-term prognosis after liver transplantation also depends on the patient's protein and energy nutritional state [4]. Thus, diagnosis of and intervention for PEM is an important issue in the clinical management of liver cirrhosis.

To improve protein malnutrition, efficacy of branched-chain amino acid (BCAA) supplementation is demonstrated [5,6]. Although there are still many criticisms against this nutritional intervention ([7–9], and for a recent comprehensive discussion, see [10]), ASPEN and ESPEN guidelines at least recommended the use of BCAA to improve hepatic insufficiency [11,12]. In several countries, parenteral BCAA formulae, enteral BCAA-enriched nutrient mixtures, or oral BCAA supplement is commercially available for cirrhotics. As an intervention for energy malnutrition, frequent meal or late evening snack has recently been recommended [11–15]. This article will particularly focus on the basic and clinical aspects of BCAA as a pharmaco-nutritional source to control PEM in patients with liver cirrhosis.

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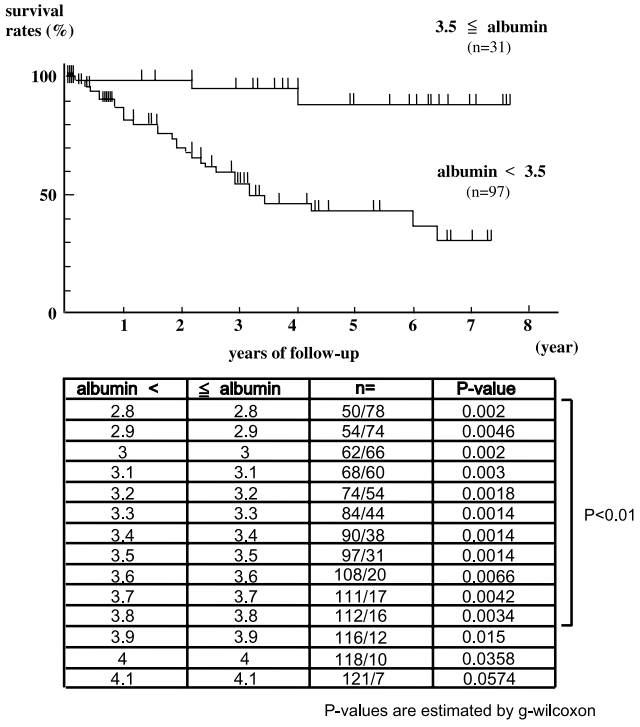
Table 1
Incidence of protein and energy malnutrition in patients with liver cirrhosis (constructed from [3])

Energy nutritional state	Protein nutritional state	
	Normal (%)	Malnourished (%)
Normal	13	25
Malnourished	12	50

Total number of patients = 128.



albumin <	≦ albumin	n=	P-value
2.8	2.8	50/78	0.002
2.9	2.9	54/74	0.0046
3	3	62/66	0.002
3.1	3.1	68/60	0.003
3.2	3.2	74/54	0.0018
3.3	3.3	84/44	0.0014
3.4	3.4	90/38	0.0014
3.5	3.5	97/31	0.0014
3.6	3.6	108/20	0.0066
3.7	3.7	111/17	0.0042
3.8	3.8	112/16	0.0034
3.9	3.9	116/12	0.015
4	4	118/10	0.0358
4.1	4.1	121/7	0.0574

P<0.01

P-values are estimated by g-wilcoxon

Fig. 1. Effect of serum albumin level on the survival of patients with liver cirrhosis. According to serum albumin at study entry, cirrhotic patients were stratified to those with hypoalbuminemia (<3.5 g/dl, $n = 97$) and those with normal albumin concentration (≥3.5 g/dl, $n = 31$). Only deaths due to hepatic failure were censored and survival rates were estimated by Kaplan–Meier method. $P < 0.05$ between two curves by the log-rank test (constructed from the study of [3]).

Mechanisms of branched-chain amino acid reduction in liver cirrhosis

Plasma amino acid analysis characterizes the patients with liver cirrhosis to have decreased BCAA [5]. There is a highly significant correlation between patients' plasma BCAA and albumin levels in liver cirrhosis, i.e., patients with low plasma BCAA have low serum albumin levels and those with high BCAA have high albumin [5]. Thus, in a similar manner to albumin as illustrated in Fig. 1, low plasma BCAA level or reduced Fischer's ratio (a molar ratio of BCAA to aromatic amino acids) also represents PEM and determines the survival of cirrhotic patients [5].

This reduction in plasma BCAA is brought about by the enhanced removal (or disappearance) of BCAA from the plasma of cirrhotic patients. The removal rate can be determined as a clearance of plasma BCAA and is demonstrated to be significantly higher in liver cirrhosis as compared with healthy control [16]. Such pronounced clearance of BCAA from plasma is explained partly by enhanced uptake and consumption of BCAA by skeletal muscles for ammonia detoxication [16] and for energy generation [17] (Fig. 2).

Hyperammonemia is a common manifestation of cirrhotic patients due to impaired hepatic capacity to detoxicate ammonia. Instead, skeletal muscles and, to a lesser extent, the brain clear blood ammonia by incorporating ammonia in the process of glutamine production from glutamate. The precursor glutamate requires BCAA for its synthesis. Thus, when exposed to hyperammonemia, skeletal muscles take up BCAA from the plasma to enhance their ability to degrade ammonia [16].

Thermogenesis in a physiological condition utilizes, of course, glucose as the most efficient energy source. In contrast, cirrhotic patients lose hepatic storage of glycogen due to liver atrophy and also get resistant to insulin in their peripheral tissues. Hence, in a cirrhotic condition, energy efficiency of glucose falls significantly, while that of BCAA rises, compensatorily, to 96% from physiological 45% [17]. Majority of such BCAA oxidation is supposed to occur in skeletal muscles and contribute to enhanced uptake of BCAA from plasma by skeletal muscles [17].

Mechanisms of branched-chain amino acid action in liver cirrhosis

Sequential effects of BCAA on albumin synthesis and secretion by hepatic parenchymal cells (HPCs), and subsequent whole body effects are summarized in Table 2. An important basic fact is that albumin mRNA is expressed solely in HPCs.

Supplementation with BCAA raises in vitro the synthesis and secretion of albumin by cultured rat hepatocytes without affecting albumin mRNA expression [18]. In an isonitrogenous condition, Fischer's ratio of the culture medium at 3–6 induces the most efficient synthesis and secretion of albumin by HPCs (plasma Fischer's ratio in normal subjects is 3–4). At Fischer's ratio below 3, the synthesis of albumin is suppressed to approximately 50% of normal condition, resulting in lower secretion of the protein. The synthesis rate is similar between Fischer's ratio of 3 and 30. However, intracellular breakdown of once-synthesized albumin (presumably preproalbumin) occurs above the ratio of 15 and again reduces the secretion of albumin by HPCs into culture media [18]. Such intracellular synthesis and degradation is supposed to be regulated at the rough surfaced endoplasmic reticulum (rough ER) level by BCAA. Possible molecular mechanism to explain this

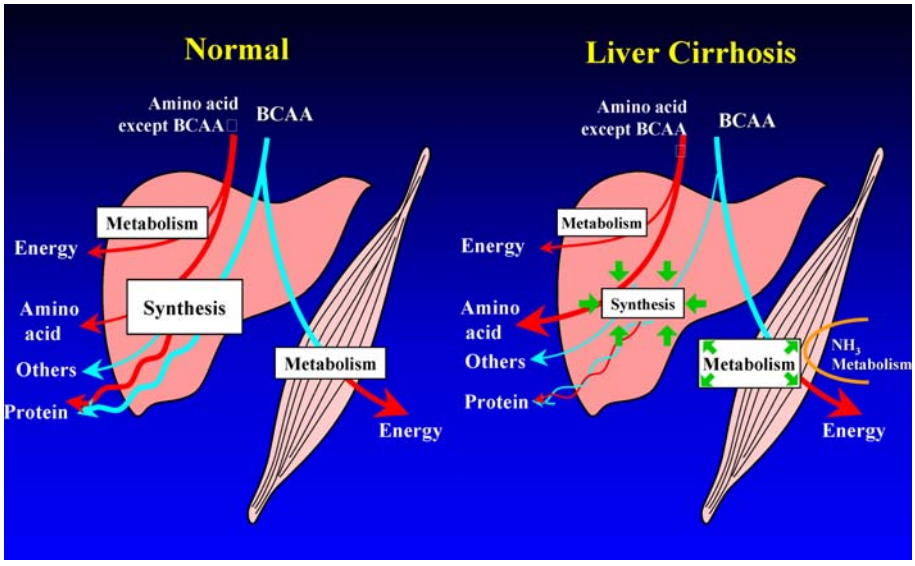


Fig. 2. Utilization of branched-chain amino acids (BCAA) by the liver and skeletal muscles in a physiological state (left panel) and in a malnourished condition with liver cirrhosis (right panel). In liver cirrhosis, increased amount of BCAA is consumed by skeletal muscles for ammonia metabolism and energy generation. Subsequently, the size of "Metabolism" pool in the muscle expands while that of "Synthesis" shrinks in liver cirrhosis as compared to those in "Normal" physiological condition.

Table 2
Sequential effects of branched-chain amino acids on in vitro and in vivo albumin synthesis and secretion

Time	Site	Effect	References
3 min	HPCs	Increased synthesis of preproalbumin	[18]
		(No effect on albumin mRNA)	[18] (HPCs), [21] (rat liver)
15–30 min	HPCs	Increased secretion of mature albumin	[18]
2 weeks	Whole body	Improved turnover kinetics of serum albumin	[19] (rat), [20] (human)
?	Whole body	Expansion of albumin pool	
2–6 months	Whole body	Rise in serum albumin level	[5,6] (human), [21] (rat)
2–4 years	Cohort	Improved survival of cirrhotics	[5,6] (human)
(6–8 months for rat)			[21]

Abbreviation: HPCs, hepatic parenchymal cells.

BCAA action is a current basic topic and will be briefly described in the next section.

Following increased secretion of albumin from HPCs, the impaired whole-body turnover kinetics of albumin, i.e., reduced synthesis and degradation rates and prolonged biological halflife, recover both in rat cirrhotic model [19] and in cirrhotic patients within 2 weeks of BCAA supplementation (Fig. 3) [20]. However, another 2–6 months supplementation with BCAA is required in liver cirrhosis to raise serum albumin (Table 2). Further continuance of BCAA supplementation benefits quality of life issues and finally improves survival [5,6,21].

Future questions (1)—energy metabolism

Recent interests focused on the timing of administration of BCAA, since daytime BCAA is usually consumed by energy generation for physical exercise of skeletal muscles in liver cirrhosis [17]. Nocturnal BCAA seem to be more favorable as a source of protein synthesis by giving higher nitrogen balance [22].

A remaining big question is whether or not energy supplementation should accompany nocturnal BCAA supplementation. Approximately 60% of the patients with liver cirrhosis is in energy malnutrition regardless of the presence or absence of protein malnutrition (Table 1). Usual energy source with ordinary BCAA content was enough, at least, to improve fuel metabolism in such cirrhotics [13]. Furthermore, Swart et al. and Chang et al. [23,24] showed that simple energy supplementation at night improved both nitrogen balance and fuel metabolism of cirrhotics. These results suggest that improved fuel supply saved amino acids from oxidation and directed them to protein synthesis. Theoretically, simultaneous supplementation with BCAA and energy might be ideal for patients with PEM. Thus, Nakaya et al. [15] used BCAA-enriched nutrient mixture, but demonstration of the specific overriding effect of BCAA has not been fully

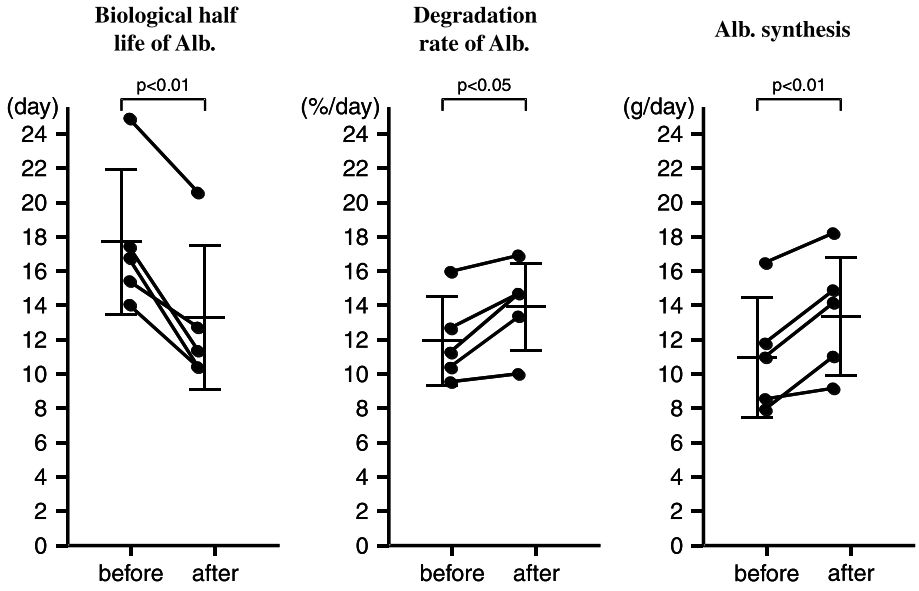


Fig. 3. Effects of 2 week-supplementation with branched-chain amino acids (BCAA) on albumin kinetics in cirrhotic patients [20]. Tracer experiment was carried out in five cirrhotic patients using iodinated human serum albumin before and after BCAA supplementation. Blood samples were drawn up to 30 days following intravenous injection of *I-albumin, serum disappearance curves of *I-albumin were constructed, and kinetic parameters were estimated by 4-compartment model analysis (from [20]).

materialized [25]. However, as suggested by Yamauchi et al. [14], it is possible that BCAA, in combination with energy, reduces muscle catabolism and, subsequently, exerts better protein sparing effect by 22:30 supplementation as compared with 19:00 supplementation. Further study will be required to determine what to provide at late evening to rescue PEM in liver cirrhosis. At present, it is safe to say that nutritional assessment of each patient will be demanded to prescribe BCAA and energy for order-made nutritional support of cirrhotics.

Future questions (2)—Molecular mechanisms of branched-chain amino acids: mTOR-dependent or independent?

Molecular mechanism of the action of BCAA, particularly that of leucine, is a focus of the recent research in this field. mTOR pathway and eIF4B pathway independently regulate protein synthesis in adipocytes, hepatocytes, and skeletal muscle cells under stimulation with leucine [26–29]. These observations suggest the use of leucine alone, instead of whole BCAA, to improve protein synthesis in several pathological conditions. This hypothesis may work when leucine or, ideally, a synthetic leucine analog is used at a pharmacological dose to activate transcription factors as mentioned above. However, administration of leucine alone at a nutrient dose will readily induce isoleucine depletion and worsen amino acid imbalance in liver cirrhosis. In contrast to protein synthesis, regulatory mechanism of protein breakdown by BCAA is still unclear. Anti-catabolic effect of leucine is recently reported to work through regulation of autophagy and lysosome-dependent proteolysis in myocytes [30]. This pathway is apparently mTOR-independent, but the responsible molecule has not been identified yet.

For the synthesis and breakdown of protein molecules, substantial amount of energy is simultaneously required in the cell [26]. This energy can be recruited endogenously or supplied exogenously in various forms as carbohydrate, fatty acid, and amino acid. When the endogenous pool of energy is not sufficient and the exogenous supply is not available, then the protein synthesis will not go on or the breakdown of body component will start to produce energy source, resulting in a worse nutritional state. Thus, correct estimation of energy requirement is essential when supplementing BCAA to improve protein malnutrition in patients. The most basic question is how much joule of energy is necessary to produce one molecule of albumin at the cellular level.

Conclusion

Experimental and clinical evidences support favorable effects of BCAA on protein malnutrition in liver cirrhosis. To raise the efficacy further, supplementation conditions including dose, time, and combinatory use of energy should be optimized by future studies.

Acknowledgments

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