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Oral Branched-Chain Amino Acids Have a Beneficial Effect on Manifestations of Hepatic Encephalopathy in a Systematic Review with Meta-Analyses of Randomized Controlled Trials[1,2]

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Abstract

Supplements with branched-chain amino acid (BCAA) have cerebral, metabolic, and nutritional effects that may benefit patients with hepatic encephalopathy (HE). We therefore conducted a systematic review on the effects of oral BCAAs compared with control supplements or placebo for patients with cirrhosis and recurrent overt or minimal HE. The quantitative analyses included data from 8 trials (n = 382 patients). Individual patient data were retrieved from 4 trials to recalculate outcomes (n = 255 patients). The mean dose of the oral BCAA supplements was 0.25 g/(kg body weight · d). Random effects meta-analysis showed that improvements in HE manifestations were registered for 87 of 172 patients in the BCAA group compared with 56 of 210 controls [risk ratio = 1.71 (95% CI: 1.17, 2.51) number needed to treat = 5 patients]. The effect of BCAAs differed (P = 0.04) for patients with overt [risk ratio = 3.26 (95% CI: 1.47, 7.22)] and minimal HE [risk ratio = 1.32 (95% CI: 0.97, 1.79)]. Subgroup, sensitivity, regression, and sequential analyses found no other sources of heterogeneity or bias. BCAA supplements had no effect on mortality or markers of nutritional status and did not induce adverse events. In conclusion, oral BCAA supplements improve manifestations of HE but have no effect on survival. J. Nutr. 143: 1263–1268, 2013.

Introduction

Hepatic encephalopathy (HE)[7] is a devastating but reversible neuropsychiatric complication of severe liver disease. The disease course fluctuates between clinically overt to minimal HE and is diagnosed with psychometric tests (1,2). The prognosis is severe. Fifty percent of patients admitted with overt HE die within 2 mo (3,4). The treatments for HE focus on precipitating factors, such as infection and bleeding, and on the reduction of ammonia, which is thought to play a pivotal role in the pathogenesis of HE (5,6). Patients with cirrhosis have a lower concentration of the essential BCAAs leucine, isoleucine, and valine. Nutritional supplements with BCAAs have been assessed as a treatment option for cirrhosis and HE. Originally, BCAAs were assessed based on the false neurotransmitter hypothesis (7), which suggests that the imbalance in blood amino acids leads to an increased efflux of cerebral aromatic amino acids with the subsequent generation of false (nonfunctional) neurotransmitters (8–11). Recent research suggests that BCAAs also play an important role in muscle metabolism leading to glutamine production from ammonia fixation and inhibition of proteolysis (12). In contrast, a bolus dose of BCAAs results in an immediate increase in ammonia concentrations (11). These complex mechanisms and the clinical differences between patients with acute or recurrent HE may underlie the difficulty in assessing the clinical effects of BCAAs.

A systematic review analyzed randomized controlled trials on BCAAs compared with no intervention, placebo, lactulose, or antibiotics (13). The review found both clinical and statistical heterogeneity between trials. The overall conclusions did not support the use of BCAA supplements. Conversely, in a subgroup analysis including 2 trials, a systematic review on nutrition for liver disease found a beneficial effect of BCAAs (14). Both reviews included oral and parenteral BCAAs. The difference between

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[2] Supplemental Table 1 and Supplemental Figure 1 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
[7] Abbreviations used: HE, hepatic encephalopathy; MD, mean difference; NNT, number needed to treat.
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the conclusions of the reviews may reflect the inclusion criteria and the number of trials included. Both reviews excluded 2 large trials (15,16). Inclusion of these trials and a subsequent high-quality trial on BCAAs compared with control diets may provide additional important information (17). A recent overview of meta-analyses updated previous reviews with inclusion of the 3 trials (18). The review described a beneficial effect of BCAAs and found that the mode of administration may influence the intervention benefit. The effect of BCAAs was identified in subgroup analyses of orally administered supplements but not in i.v. products. Additional patient and intervention characteristics may influence the intervention benefit. We therefore conducted this systematic review on oral BCAAs supplements compared with placebo or control diets for manifestations of recurrent HE with detailed analyses of potential sources of heterogeneity.

Methods

This review was based on a protocol that was prepared according to recommendations described in the Cochrane Handbook (19) and reported based on the preferred reporting items for systematic reviews and meta-analyses statement (20). The primary objective was to evaluate the beneficial and harmful effects of oral BCAAs compared with no intervention, placebo, or control diets on HE manifestations, mortality, nutritional status, and adverse events in patients with recurrent HE. Trials were identified via electronic and manual searches. The electronic searches were performed in The Cochrane Library [using the terms branched-chain AND (encephalopath* OR 'liver disease*' OR cirrho*)], MEDLINE, EMBASE, and Science Citation Index based on searches developed with the help of the Cochrane Hepato-Biliary Group Trial Search Coordinator (last search update, December 2012). Manual searches of reference lists in relevant papers, specialist journals, and conference proceedings were also performed. Additional trials were sought through the WHO Trial Register and via correspondence with experts. Trials identified from literature searches were listed and the trials included were selected using the criteria described above. Excluded trials were listed with the reason for exclusion. All authors participated in the selection of trials for inclusion.

Trial and patient inclusion criteria.

Randomized controlled trials were included irrespective of blinding, publication status, or language. In view of the fluctuating nature of HE, we used the first period of crossover trials. Patients with recurrent HE were included regardless of whether the type was classified as recurrent overt or minimal. The underlying liver disease could be acute or chronic. For trials in which only a proportion of patients had HE at baseline (e.g., trials on patients with previous episodes of HE), individual patient data were retrieved. Subsequently, the trial results were recalculated after the exclusion of patients who did not have HE at inclusion. Accordingly, only data on patients with HE at baseline were included in our analyses. The methods used for diagnosing HE included psychometric tests (e.g., the digit symbol test, number connection test/Trail Making Test, part A, number revision test, or the motor performance test battery) or clinical scores (e.g., the Portal-Systemic Encephalopathy index or the West-Haven criteria). The interventions assessed were oral BCAAs (including BCAA-enriched preparations) compared with no intervention, placebo, isocaloric supplements, or isonitrogenous supplements or diets. Co-interventions, such as lactulose, were permitted if allocated to both the intervention and the control groups.

Outcome measures and extraction of data.

The primary outcome measure was the number of patients with clinically important improvements in HE manifestations. The secondary outcome measures were all-cause mortality, markers of nutritional status [serum creatinine, serum albumin, nitrogen balance, mid-arm or mid-calf muscle circumference, and adverse events (number and type of adverse events and losses to follow-up)]. Four authors (L.L.G., G.D., M.B., and N.R.) independently extracted data. Outcomes were recalculated based on individual patient data from 3 investigator-initiated trials (16,17,21) and 1 trial funded by a pharmaceutical company (15).

Assessment of bias control.

The randomization methods (selection bias) were extracted as the primary measure of bias control (22). The allocation sequence generation was classed as adequate if it was based on computer-generated random numbers, a table of random numbers, or similar, and the allocation concealment was adequate if it was performed using a central independent unit with coded drug containers of identical appearance; serially numbered, opaque, sealed envelopes; or similar. We also extracted data on blinding (performance and detection bias), whether the trial achieved the planned sample size or was terminated early, and whether all randomized patients were accounted for (attrition bias). Outcome reporting (reporting bias) was assessed by the extent to which clinically relevant outcome measures were reported. Differences between trial protocols and subsequent reports were evaluated as an additional marker of reporting bias.

Data analysis.

The analyses were performed using RevMan version 5 (Nordic Cochrane Centre), Stata version 12 (Stata Corp), and Trial Sequential Analysis (Cochrane Hepato-Biliary Group). The primary meta-analyses were performed using random-effects models due to an expected clinical heterogeneity. Individual patient data were performed using a 2-stage approach as previously recommended (23). In the first stage, outcomes from individual trials were analyzed for patients with HE at baseline. In the second step, the summary statistics of each of these individual trials were combined to provide a pooled estimate. Dichotomous data were analyzed using risk ratios. The number needed to treat (NNT) was calculated using the risk difference and was defined as the number of patients who need to be treated to prevent one additional harmful outcome or to achieve one additional beneficial outcome. Continuous data were analyzed using mean differences (MDs). The I^2 values were reported as a measure of heterogeneity, with values from 40 to 60% defined as moderate heterogeneity, values between 60 and 75% as substantial heterogeneity, and values >75% as considerable heterogeneity. I^2 values < 40% were considered unimportant (24).

The risk of publication bias and other biases was assessed using regression analysis (Egger's test). For the primary outcome measure, subgroup, sensitivity analyses, and regression analyses were performed to analyze the influence of patient, intervention, and trial characteristics. The subgroup analyses compared patients stratified by the type of HE (minimal or chronic), type of underlying liver disease (alcohol or chronic viral hepatitis), type of control intervention (isonitrogenous, isocaloric, or placebo), and type of data (recalculated based on individual patient data or extracted from trial reports). The test for subgroup differences was calculated and the results presented as P values. Random-effects meta-regression was performed to evaluate the effect of the dose of BCAAs. For trials assessing a weight-adjusted dose of BCAAs, the daily dose of BCAAs was calculated for a body weight of 65 kg. Sensitivity analyses were performed to evaluate the influence of bias control (including only trials in which randomization was classed as adequate) and the statistical model (repeating the primary meta-analysis using a fixed effect model). We also performed a post hoc sensitivity analysis excluding trials in which a proportion of patients had transjugular intrahepatic shunts. Sequential analyses were performed to evaluate the robustness of the overall results after adjusting for multiple testing (25). The sequential analysis was considered to support the overall result if the monitoring boundary crossed the conventional boundary. The analysis was performed using a risk ratio random-effects model with conventional 95% CIs, 80% power, and the α set to 5%. The risk ratio reduction was set to 65%, the control group incidence to 27%, and the (model-based) heterogeneity to 51%.

Results

The electronic database searches generated 528 hits (**Supplemental Fig. 1**). Nineteen additional records were identified via manual searches. After excluding 354 duplicates and clearly irrelevant references, 76 references were retrieved for further

assessment. Twenty-eight references to 13 trials were excluded, because they evaluated the effect of i.v. BCAAs (n = 8), compared different BCAA regimens (n = 3), or were quasi-randomized (n = 2). The remaining 17 references referred to 8 randomized controlled trials (**Table 1**) that were then included in our analyses (15–17,21,26–29). Outcomes were recalculated for 255 patients from 4 trials [3 investigator initiated (16,17,21) and 1 trial with for-profit funding (15)]. For the remaining trials (n = 127 patients), data were available and extracted from published reports.

The trials were published from 1985 to 2011. All trials were published in English language journals. One trial was published in abstract form (27) and the remaining trials as full-text articles. All participants gave written informed consent and the studies were approved by the local ethics committees. The proportion of patients with alcoholic liver disease ranged from 8 to 100% and the proportion with viral hepatitis from 0 to 81%. The proportion of patients with transjugular intrahepatic portosystemic shunts ranged from 0 to 15%.

Included patients had cirrhosis and recurrent HE that was classified as overt (4 trials; n = 168 patients) or minimal (4 trials; n = 214 patients). The diagnostic criteria were based on composite scores (including the portal-systemic HE index and the West-Haven criteria), psychometric tests (including validated tests, e.g., the digit symbol and number connection test), ammonia concentrations, and electroencephalography. Clinically important improvement in HE manifestations was defined based on the portal-systemic HE index, West-Haven criteria, and psychometric tests focusing on the Reitan Trail-Making Test.

The treatment duration varied from 3 wk to 2 y. The mean dose of the oral BCAA supplements was 0.25 g/(kg body weight · d) (**Table 2**). The control groups received placebo or isonitrogenous and/or isocaloric supplements.

Bias control. The trial published in abstract form (27) did not describe how the patients were randomized (**Supplemental Table 1**). The allocation concealment was classed as adequate in all remaining trials. No differences in the baseline characteristics of the BCAA or control groups were identified. Two trials were performed without blinding. The remaining trials were conducted with blinding of investigators and patients or outcome assessors. Two trials did not account for losses to follow-up or withdrawals. The remaining trials accounted for all patients randomized irrespective of compliance or follow-up. There was no evidence of reporting bias. No other apparent biases were identified. For 3 trials, sample size calculations were performed and the required sample size was achieved. Sample size calculations were not reported for the remaining trials. None of the trials included were described as being prematurely terminated.

The effect of BCAAs on HE manifestations. Data on the number of patients with clinically important improvements in HE manifestations were available from 7 trials (**Fig. 1**). The number was 87 of 172 patients in the BCAA group compared with 56 of 210 controls. Random-effects meta-analysis showed that the oral BCAA supplements had a beneficial effect on this outcome measure [risk ratio = 1.71 (95% CI: 1.17, 2.51); NNT: 5 patients]. The heterogeneity between trials was moderate (I^2 = 43%). The result was stable when excluding the trial published in abstract form [risk ratio = 1.56 (95% CI: 1.16, 2.11). There was no evidence of bias in the regression analyses (Egger's test P = 0.59). Subgroup analyses showed that the effect of BCAA was different (test for subgroup differences P = 0.04) in overt HE [risk ratio = 3.26 (95% CI: 1.47, 7.22)] and minimal HE [risk ratio = 1.32 (95% CI: 0.97, 1.79)]. The effect of BCAAs did not differ in subgroups of trials with different control interventions [isonitrogenous control risk ratio = 1.90 (95% CI: 1.01, 3.30), nonisonitrogenous control risk ratio = 1.53 (95% CI: 0.95, 2.47); test for subgroup differences P = 0.13]. There was no difference (test for subgroup differences P = 0.87) between trials for which data were recalculated based on individual patient data [risk ratio = 1.53 (95% CI: 1.12, 2.09)] or extracted from trial reports [risk ratio = 4.58 (95% CI: 1.59, 13.23)]. In random-effects meta-regression, the overall result was not associated with the type of the underlying liver disease (alcoholic liver disease P = 0.57 or viral liver disease P = 0.16), the dose of BCAAs (P = 0.43), or the duration of therapy (P = 0.35). Sensitivity analyses confirmed that the beneficial effect of BCAA supplements was retained when trials with adequate randomization were included [risk ratio = 1.56 (95% CI: 1.16, 2.11)] and when the meta-analysis was repeated using a fixed-effect model [risk ratio = 1.84 (95% CI: 1.41, 2.39)]. Post-hoc analyses showed that the effect of BCAAs remained stable after exclusion of trials including patients with transjugular intrahepatic shunts [risk ratio = 1.76 (95% CI: 1.35, 2.29)] and when excluding the trial with data provided by the pharmaceutical company [risk ratio = 2.03 (95% CI: 1.51, 2.73)]. In the sequential analysis, the monitoring boundary crossed the conventional boundary after 4 trials. Thus, the sequential analysis confirmed the robustness of the overall result.

The effect of BCAAs on secondary outcome measures. Data on mortality were retrieved from 7 trials (Fig. 1). Fifteen of 148 patients in the BCAA and 21 of 189 patients in the control groups died [risk ratio = 0.90 (95% CI: 0.50, 1.63)]. We retrieved data on post-treatment albumin from 3 trials (16,17,21) and found no difference between the BCAA and the control groups [MD = 0.60 g/L (95% CI: −0.90, 2.09 g/L); I^2 = 55%].

TABLE 1 Characteristics of included patients[1]

Trial	Clinical HE	Minimal HE	Patients in BCAA and control groups	Alcoholic liver disease	Viral hepatitis
	%		*n*, *n*	%	
Hayashi et al., 1991 (27)	100	0	35, 32	58	9
Horst et al., 1984 (28)	41	0	17, 20	38	8
Marchesini et al., 1990 (21)	100	0	30, 34	56	41
Marchesini et al., 2003 (16)	0	74	33, 79	21	68
Muto et al., 2005 (15)	6	0	27, 12	8	81
Plauth et al., 1993 (29)	0	100	12, 11	88	12
Egberts et al., 1985 (26)	0	100	11, 11	86	14
Les et al., 2011 (17)	0	34	18, 22	36	53

[1] Patients included in randomized controlled trials. HE, hepatic encephalopathy.

TABLE 2 Dose and duration of BCAAs and control interventions[1]

Trial	Dose of BCAAs	Control	Additional standard diet[2]	Treatment duration
Hayashi et al., 1991 (27)	11 g/d	Isonitrogenous and isocaloric supplement	No	3 wk
Horst et al., 1984 (28)	6.92 to 20.92 g/d	Isonitrogenous and isocaloric supplement	Protein 20 g/d	4 wk
Marchesini et al., 1990 (21)	0.24 g/(kg · d)	Isonitrogenous supplement (casein)	No	3 mo
Marchesini et al., 2003 (16)	14.4 g/d	Isonitrogenous (lactoalbumin) or isocaloric (maltodextrin) supplements	Protein 0.8 g/(kg · d) and 0.30 kcal/(kg · d)	1 y
Muto et al., 2005 (15)	12 g/d	Isonitrogenous and isocaloric supplement	No	2 y
Plauth et al., 1993 (29)	0.25 g/(kg · d)	Placebo	No	8 wk
Egberts et al., 1985 (26)	0.25 g/(kg · d)	Isonitrogenous supplement (casein)	Protein 1 g/(kg · d) and 35 kcal/(kg · d)	4 wk
Les et al., 2011 (17)	30 g/d	Isocaloric supplement (maltodextrin)	Protein 0.7 g/(kg · d) and 35 kcal/(kg · d)	56 wk

[1] Intervention regimens assessed in included randomized controlled trials.
[2] The standard diets were administered in addition to the BCAA and control supplements.

One trial assessed nitrogen balance (21) and found no difference between groups [MD = 1.72 (95% CI: 0.78, 2.66)]. No additional analyses on nutritional measurements were possible. The adverse events that were registered included nausea and diarrhea, with no difference between the groups [risk ratio = 1.79 (95% CI: 0.76, 4.24); I^2 = 2%]. The number of dropouts and withdrawals were also similar between the groups: 12 of 127 patients in the BCAA group and 15 of 148 patients in the control groups [risk ratio = 0.49 (95% CI: 0.23, 1.02); I^2 = 0%].

Discussion

This systematic review found that oral BCAA supplements improved the manifestations of recurrent HE in patients with cirrhosis. The NNT was 5, suggesting that the size of the intervention benefit is clinically relevant. No further beneficial or detrimental effects on mortality, nutrition, or adverse events were identified.

There was a clinical variation in the terminology and methods used to diagnose and classify HE in the trials included. The main limitations of our review are the heterogeneity of the clinical assessment and the populations treated with BCAAs. We attempted to adjust our analyses to account for these limitations and the approach we used was oriented to obtain maximal reasonable information from the present knowledge. The heterogeneity makes it difficult to make more specific conclusions regarding the patient population that is most likely to benefit from the treatment. Further research focusing on the identification of subgroups that benefit from the treatment and the effect of BCAAs on the prevention of HE is needed.

Some trials described included patients as having latent or chronic HE (26,29). Other trials included a proportion of patients with cirrhosis and clinical (15) or minimal HE (16,17). Based on the current terminology recommendations (30), the patients included in this review may be categorized as having recurrent HE. The definition of improvements in HE varied. Part of the variability is likely to reflect changes in clinical practice over time. The initial trials assessed HE based on the portal-systemic encephalopathy index (21,28), whereas later trials used the West-Haven criteria (15). Trials on minimal HE used a range of psychometric tests, with one trial focusing on driving capabilities (29) and other trials on Trail-Making or symbol-digit tests (16,17). For a number of patients, the improvement denoted a complete resolution of HE. For other patients, the improvement was incomplete but still assessed as clinically important. Such improvements are associated with improved quality of life (31).

This review is based on randomized clinical trials, and the overall result was stable to bias assessments and did not appear to depend on control interventions or the etiology of the underlying liver disease. Unlike previous meta-analyses (13,14), this systematic review includes data on outcomes that were recalculated based on individual patient data. There was no difference between outcomes of trials for which data were extracted from trial reports and trials for which individual patient data were used to recalculate trial results. Likewise, exclusion of data provided by pharmaceutical companies had no clear influence on the overall result. In fact, the industry-funded trial (15) found no clear benefit of BCAAs on improved HE, whereas investigator-initiated trials found that BCAAs improved HE manifestations (16,17,21). The combined evidence suggests that our overall result is reasonable and may be used to guide clinical recommendations as well as to justify the effort of larger and better-conducted studies.

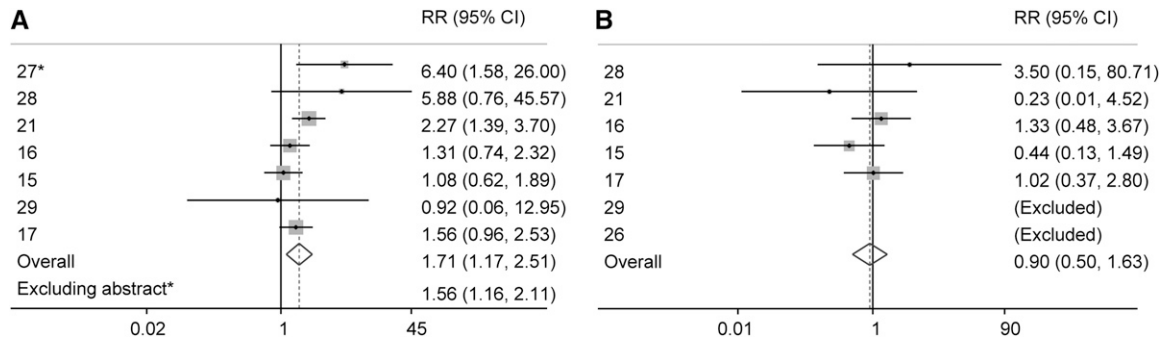

FIGURE 1 Forest plot of random effects meta-analysis on BCAA supplements compared with placebo or control diets for improvement in HE manifestations (*A*) and mortality (*B*). The plot shows the overall result including all trials and *the result after exclusion of a trial published in abstract form. HE, hepatic encephalopathy; RR, risk ratio.

The fact that some of the trials included were published several years ago may be important. The terminology, diagnostic criteria, and management of complications of cirrhosis have changed since the 1980s. The use of antibiotics, endoscopic interventions, and vasoactive drugs for variceal bleeding and the use of terlipressin and albumin for hepatorenal syndrome are important therapeutic improvements (32–35). These improvements have increased survival, which means that the population of patients with cirrhosis at risk of developing HE is growing, which itself increases the requirement for interventions that alleviate HE manifestations.

Hepatic malnutrition involves diminished intake, increased requirements, and an altered amino acid metabolism. Malnutrition is an important adverse prognostic factor in cirrhosis. Previous studies have discovered that BCAAs improve insulin resistance (35) and metabolic profile (assessed by protein retention and respiratory quotients) (36,37). This review uncovered sparse amounts of data on the metabolic effects of BCAA supplements, and no differences in nitrogen balance or albumin between BCAA and control groups were noted. Furthermore, the potential benefit of BCAAs on nutrition cannot explain the demonstrated effect in short-term trials. Possibly the short-term effect is explained by an action on the brain, muscle, liver, or immunological system. Several mechanisms of action are hypothesized. BCAA facilitate ammonia detoxification by supporting glutamine synthesis in skeletal muscle and the brain, normalize plasma amino acid concentrations, and decrease brain influx of aromatic amino acids (8). Anaplerotic reactions with conversion of glutamate may be important, as is the role of BCAAs as nitrogen donors for the synthesis of neurotransmitters in brain (36). Furthermore, research data suggest that BCAAs improve the immune response (38–40). Accordingly, the exact mechanism of action of BCAAs on HE still needs to be clarified.

In this review, most trials assessed the recommended daily dose of oral BCAA supplements (0.25 g/kg). The dose should be sufficient to achieve an effect. The data did not allow for specific comparisons between different dosing regimens, but it is not likely that a higher response would be achieved if higher doses were used. Likewise, we were unable to determine the optimal duration of therapy. The included patients had chronic liver disease and the need for supplemental BCAAs is likely to continue unless the degree of liver damage is reduced. We found no clear difference between trials with short- or long-term intervention regimens. Although none of the trials evaluated HE manifestations after the end of treatment, long-term effects are unlikely to exist after treatment is stopped.

The results of this review may be compared with a recent trial of rifaximin (a poorly absorbed antibiotic) on the prevention of HE relapse in patients with cirrhosis (32). The trial reported a beneficial effect of rifaximin with an NNT of 4 patients. The size of the effect appears comparable with BCAAs. Both interventions improved the quality of life (16,37). The fact that the target organs and the mechanism of action differs between the 2 treatments suggests that there may be an additive effect when they are combined.

Our results show a convincing beneficial effect of oral BCAAs on the manifestations of recurrent BCAAs in cirrhosis. This finding concurs with the European Society for Clinical Nutrition and Metabolism guideline (38) that recommends BCAA-enriched formulae for patients who develop HE during enteral nutrition. The combined evidence supports the use of BCAA supplements in clinical practice and forms a basis for future research.

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