Evidence Analysis Library Research Project

EAL question: What is the evidence to support the use of supplementing BCAA in patients with cirrhosis to 1) prevent further liver damage or improve liver function; 2) prevent progression to ESLD; 3) improve nutritional status?

Critical Appraisal of Each Study

Quality Criteria Checklist: Primary Research RELEVANCE QUESTIONS	
Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?	Yes
Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	Yes
Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.	
VALIDITY QUESTIONS	
1. Was the research question clearly stated? 1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified? 1.2 Was the outcome(s) (dependent variable(s)) clearly indicated? 1.3 Were the target population and setting specified?	1.1 Yes 1.2 Yes 1.3 Yes
2. Was the selection of study subjects/patients free from bias? 2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? 2.2 Were criteria applied equally to all study groups? 2.3 Were health, demographics, and other characteristics of subjects described? 2.4 Were the subjects/patients a representative sample of the relevant population?	 2.1 Yes 2.2 Yes 2.3 Yes 2.4 Yes
13. Were study groups comparable? 13.1 Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) 13.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? 13.3 Were concurrent controls used? (Concurrent preferred over historical controls.) 13.4 I If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? 13.5 I If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	 13.1 Yes 13.2 Yes 13.3 Yes 13.4 N/A 13.5 Yes

13.6 I If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	13.6 N/A
14. Was method of handling withdrawals described? 14.1 Were follow up methods described and the same for all groups? 14.2 Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) 14.3 Were all enrolled subjects/patients (in the original sample) accounted for? 14.4 Were reasons for withdrawals similar across groups?	14.1 Yes 14.2 Yes 14.3 Yes 14.4 No

Citation:	Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, Fanelli F, Abbiati R. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. *Gastroenterology*. 2003;124:1792-1801.
Study Design:	Multicenter, double-blind, randomized control trial
Class:	A
Quality Rating:	+
Research Purpose:	The purpose of this research was to determine if supplementation with BCAA in patients with advanced cirrhosis would improve selected primary and secondary markers of overall health.
Inclusion Criteria:	• Diagnosis of liver cirrhosis documented by histology and confirmed by laboratory data. • Child-Pugh score greater than or equal to 7 • Sonographic and endoscopic evidence of portal hypertension • Informed consent
Exclusion Criteria:	• Active alcohol consumption • Overt hepatic encephalopathy • Refractory ascites • Reduced renal function • Child-Pugh score greater than or equal to 12 • Suspected hepatocellular carcinoma • Previous poor compliance to pharmacologic treatment and nutritional counseling • Patients already on waiting list or being considered for liver transplantation
Description of Study Recruitment:	15 centers treating liver disease were selected and each center recruited 12 patients with advanced liver cirrhosis of an etiology in a 6-month period.
Protocol:	3 groups of patients were randomly assigned to 1 of 3 different treatments: BCAA, lactoalbumin, or maltodextrins. Data was collected at baseline and then every 3 months for 12 months. Compliance with treatment was assessed at each scheduled office visit by counting the number of unused supplement packets.
Intervention	3 types of nutritional supplementation were supplied in 10 gram packets. • BCAA (active treatment) 2.4 g/packet totaling 14.4 g/day and 37.5 kcal. • Lactoalbumin (L-ALB) 2.1 g L-ALB with 4.0 g saccharose and 3.0 g mannitol totaling 33.6 kcal/day • Maltodextrin (M-DXT) 2.4 g M-DXT with 6.7 g saccharose totaling 34.9 kcal Patients were kept on a self-selected diet containing at least 30 kcal and 0.8 g protein per kg bodyweight per day.

Statistical Analysis	• StatView 5.0 • Primary outcomes were measured on an intent-to-treat basis. Secondary outcomes were measured by means of repeated-measures analysis of variance (ANOVA) or paired t test. Unpaired t test, contingency test, and Fisher exact test were used when appropriate to compare groups at baseline and at the end of the study period.
Data Collection Summary: **Timing and method of measurements**	• Routine laboratory and clinical investigations were measured at baseline and then at 3 month intervals • Anthropometric measurements were taken at baseline • Self-administered questionnaires were administered to evaluate anorexia, dietary intake, and health-related quality of life at baseline and then at 6 and 12 months.
Dependent Variables	• Number of days spent in hospital • Triceps skinfold thickness • Albumin and prothrombin activity levels • Total bilirubin levels • Presence and severity of ascites • Encephalopathy score • Prevalence of anorexia • Physical functioning • Emotional state
Independent Variables	• BCAA treatment • L-ALB treatment • M-DXT treatment
Description of Actual Data Sample:	
Initial n	n=174. 110 males and 64 females
Final n	n=115
Age	Mean age 60 years ± 1
Ethnicity	Not described
Anthropometrics/subject characteristics	All subjects were similar in terms of etiology, liver function, clinical signs of portal hypertension, and hospital admission rate.
Location	Multicenter; Italy
Summary of Results **Primary findings**	***See chart 1.1 below • Hospital admission rate was non-significantly reduced in the BCAA group and was increased in the L-ALB and M-DXT groups. • No significant differences in the encephalopathy score were observed. • Patients treated with BCAA showed a better scoring of health with the percent of patients scoring their health as poor decreasing from 19% to 3%. There was no change in the L-ALB or M-DXT groups.
Author Conclusion:	This study showed that there are benefits to routinely supplementing BCAA in patients with advanced cirrhosis, particularly in subjects compliant with long-term treatment.

***Primary findings 1.1

Dependent Variable	**BCAA**	**L-ALB**	**M-DXT**
Total number of days spent in hospital	195	327	520
P=0.038			
Triceps skin fold thickness			
Before	10.9 ± 0.8 mm	11.2 ± 0.8	12.0 ± 0.9
After	12.1 ± 0.9 mm	Worse	worse
P=0.041			
Prothrombin and albumin	slightly improved	slightly improved	slightly improved
Total bilirubin	decreased	no change	increased
P=0.0012			
Prevalence/severity of ascites	reduced	No change	No change
P=0.011			
Child-Pugh score (measure of ascites)			
Before	9.1 ± 0.3	8.5 ± 0.3	8.7 ± 0.3
After	7.9 ± 0.3	8.0 ± 0.3	8.4 ± 0.3
P value	P<0.0001	P=0.115	P=0.213
Prevalence of anorexia			
Before	21 of 40	unchanged	unchanged
After	10 of 40		
P value	P=.0014		
Physical functioning			
Before	67% ± 4%		
After	73% ± 3%		
P value	0.023		
Emotional state			
Before	50% ± 6	unchanged	unchanged
After	63% ± 6%		
P value	0.0171		

Quality Criteria Checklist: Secondary Research RELEVANCE QUESTIONS

1.Will the answer if true, have a direct bearing on the health of patients?	Yes
2. Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3. Is the problem addressed in the review one that is relevant to dietetics practice?	Yes
4. Will the information, if true, require a change in practice?	Yes
VALIDITY QUESTIONS	
1. Was the question for the review clearly focused and appropriate?	Yes
2. Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described?	Unclear no
3. Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	No, yes, unclear
4. Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes no
5. Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes, unclear
6. Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes yes
7. Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	No, Yes/unclear Unclear Yes Yes N/A
8. Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes N/A
9. Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes Yes
10. Was bias due to the review's funding or sponsorship unlikely?	no

Citation: Marchesini G, Marzocchi R, Noia M, Bianchi G. Branched-chain amino acid supplementation in patients with liver dieases. *J Nutr.* 2005; 135:1596s-1601s	
Study Design: Narrative Review	
Class: R	
Quality Rating: Ø	
Research Purpose: To review the results of BCAA supplementation in liver disease relative to the amount of amino acid supply.	
Inclusion Criteria: • Studies must focus on liver patients and BCAA supplementation	
Exclusion Criteria: • Individual studies used in review differed in their exclusion criteria	
Description of Study Protocol:	• No specific search procedures were mentioned. It appears that this review was all inclusive. • The quality of every study used in the review was not specifically addressed. Important indicators of study quality such as number of participants and length of study are noted in the table of randomized control trials. Also, whenever specific studies are mention in the narrative the quality of the study is addressed. • Most of the studies reviewed looked at survival, encephalopathy and/or nitrogen balance. A few studies also looked at anthropometry and disease progression.
Data Collection Summary:	• 19 randomized controlled trials using BCAA treatment for cirrhosis were compiled and compared for their study type, number of patients, study length, dosage of BCAA, control, outcomes measured and statistically significant results. • There was no combination of data or meta-analysis. • The narrative also used review studies and Meta-analysis on the subject to reach its final conclusion. • Control treatments in the randomized control trials varied widely and included lactulose, glucose, standard amino acids, dextrose, neomycin, carbohydrates, casein, lactoalbumin, maltodextrin, and dietary proteins.
Description of Actual Data Sample:	• The number of patients in the randomized control trials varied from as little as six to as many as 176. Attrition rate is only specifically mentioned for a few trials. • Age and ethnicity were not described
Summary of Results:	• Nitrogen Balance: three of six studies showed statistical significance • Survival: two of seven studies showed statistical significance, one study's result was dubious • Encephalopathy: six of 18 studies showed statistical significance, one result was dubious

Author Conclusion: There are many potential benefits to cirrhotic patients in using BCAA including down regulation of protein metabolism, nitrogen balance improvement and clinical outcomes such as improving from hepatic encephalopathy and facilitating liver regeneration. In I.V patients it appears that BCAA enriched formulas are better than pure BCAA infusions. It also appears that oral supplementation should only be used in patients that are not getting 1g/kg of protein in their diet so as not to increase the risk of encephalopathy. The issue of whether there is enough evidence to apply these findings to practice is still not resolved. This issue is only further complicated by the need for dose finding studies and studies using individual BCAA's.	
Review Comments:	*This article provides very useful background information on the mechanisms of BCAA and the inherent problems that exist in all clinical trials using BCAA such as the side effects of BCAA powders. It's limitations is that it does not detail any of its methods or study protocol used in determining which studies it reviewed and which studies were considered in drawing conclusions.*
Funding Source	The review was conducted by the university of Bologna, Italy and was presented via funding by the International council of Amino Acid Science.

Step 4: Summarize Evidence

Study	Author, Year, Study Design, Class Rating	Study Type/Purpose	Study population	Intervention	Outcomes	Conclusions
Primary	Marchesini G, Bianchi G, et al, 2003 Study Design: Double-blind, randomized trial Class A Rating: +	To determine if supplementation with BCAA in patients with severe liver cirrhosis would improve primary and secondary parameters reflecting overall patient health.	**Treatment** N=59, mean age 60 ± 1, most had severe liver disease **Control** N=115, mean age 60 ± 1, most had severe liver disease	3 types of nutritional supplementation were supplied: BCAA, Lactoalbumin, or Maltodextrin in 10 gram packets. Patients were kept on a self-selected diet containing at least 30 kcal and 0.8 g protein per kg bodyweight per day.	Hospital admissions were lower for the BCAA group as compared to the control group. Triceps skinfold increased for the BCAA group, but worsened in the control group. Total bilirubin decreased for BCAA group, was unchanged in the L-ALB group and increased in the M-DXT group. Prevalence of ascites and anorexia was decreased in the BCAA group only. Physical functioning and emotional state was improved in the BCAA group but not the control groups.	This study showed that there are benefits to routinely supplementing BCAA in patients with advanced cirrhosis, particularly in subjects compliant with long-term treatment.
Secondary	Marchesini G, Marzocchi R, Noia M, Bianchi G. 2005; Narrative review Class R Rating Ø	To review the results of BCAA supplementation in liver disease relative to the amount of amino acid supply.	The number of patients in the randomized control trials varied from as little as six to as many as 176. Age and ethnicity were not described	19 randomized controlled trials using BCAA treatment for cirrhosis were compiled and compared for their study type, number of patients, study length, dosage of BCAA, control, outcomes measured and statistically significant results. The narrative also used review studies and Meta-analysis on the subject to reach its final conclusion.	Nitrogen Balance: three of six studies showed statistical significance Survival: two of seven studies showed statistical significance, one study's result was dubious Encephalopathy: six of 18 studies showed statistical significance, one result was dubious	There are many potential benefits to cirrhotic patients in using BCAA. In I.V patients BCAA enriched formulas are better than pure BCAA infusions. Supplementation should only be used in patients not getting 1g/kg of protein in their diet so as not to increase encephalopathy risk. There is not enough evidence to apply these findings to practice there is a need for dose finding studies and studies using individual BCAA's.

Evidence Summary Narrative

Two reports were used in this evidence analysis; one primary research paper pertaining to a specific double-blind, randomized trial and one secondary research paper that is a narrative review of all of the current research on this subject. The primary research was a multi-center trial involving 115 patients with advanced liver cirrhosis. Most patients had severe liver disease which had required hospital admission during the previous year in nearly one half of the cases. Baseline measurements were taken to assess each patient's physical and emotional health. Each patient was assigned to either a treatment or control group. The treatment group consumed a BCAA supplement and the two control groups consumed either a L-ALB or M-DXT supplement. No formal diet was prescribed, but all patients were kept on a self selected diet containing at least 30 kcal and 0.8 grams of protein per kilogram of bodyweight per day. Clinical and laboratory investigations were repeated at 3 month intervals and adverse events, hospital admissions and therapeutic changes were also noted at this time.

The secondary research report summarized the current literature involving the evidence of the mechanisms for BCAA action. The authors also looked at 19 Randomized controlled trials (RCT) with a wide range of variables. Study durations ranged from as little as two days to as long as 12 months. As many as 11 different control treatments were compared to BCAA supplements. The amounts and methods of BCAA supplementation also varied in all of these studies. Included in this report as well were the results of a Cochrane review looking at encephalopathy and survival outcomes of BCAA trials.

The results of the primary study showed that the group consuming the BCAA supplement had significantly greater improvements in both physical and emotional parameters compared to those in the two control groups. The following parameters were significantly improved in the patients in the BCAA group, but not in the patients in the two control groups: total number of days spent in the hospital, triceps skinfold thickness, albumin, prothrombin, and bilirubin levels, liver function test, prevalence and severity of ascites, prevalence of anorexia, physical functioning and emotional status. Results from the Reitan test showed that there were no differences in the encephalopathy score.

The mechanisms for BCAA action were summarized by the secondary research article as follows: BCAA stimulate hepatocyte growth factor; thus increasing liver regeneration and preventing further loss of liver function by compensating for hepatocyte death. BCAA supplementation can also help alleviate PEM in cirrhotic patients, who are generally hypermetabolic, by downregulating protein metabolism and improving nitrogen balance. BCAA catabolism is not restricted to the liver like other Amino acids so it's availability in the general circulation encourages protein synthesis.

Of the 19 randomized control trials in the secondary research, seven trials measured survival as an outcome; two of these trials found a significant difference in survival for patients given BCAA over the control. 18 trials measured markers of encephalopathy with six of those showing a significant improvement. Six trials measured nitrogen balance and three of those showed a significant improvement. Clearly many studies have shown statistically significant benefits of BCAA supplementation in liver disease. This parallels the significant benefits shown in the primary research. The one difference between the two reports being that the primary research could not prove a significant change in encephalopathy markers whereas the secondary research cites a Cochrane review that did just that. According to the Cochrane review, the data from 11 RCT were meta-analyzed and this confirmed the significance of BCAA supplementation benefits on encephalopathy.

When comparing the two articles, both articles found that supplementation with BCAA in patients with advanced cirrhosis can help improve liver function, prevent further liver damage, and improve the patients overall nutritional status. Both articles had individual limitations in applying the results to practice and both suggested the need for further research.

Step 5: Conclusion Statement

Current evidence shows that the use of BCAA may be useful in preventing further liver damage, improving liver function, preventing progression to ESLD, and improving nutritional status in patients with cirrhosis. This evidence however, is not conclusive to prove that consumption of BCAA supplements will help all patients with cirrhosis. Recommendations for implementing the research that does exist follows.

According to the secondary research, BCAA supplementation would be most beneficial for patients that cannot achieve a daily protein intake of 1g/day either because of anorexia or restriction based on encephalopathy. The recommendation for IV administration is to use a BCAA enriched formula rather than pure BCAA. In oral administration it is recommended to limit the BCAA supplementation to amounts doubling the usual dietary intake. Exact dosages have yet to be determined.

If considering oral supplements, nutrition professionals should asses the patient's willingness to comply with consistent consumption of a BCAA supplement. The treatment should only be prescribed if the patient shows positive signs of compliance and if after the treatment, the patient shows signs of improvement.

If the dietitian is uncomfortable recommending use of the supplement based on the limited evidence available, the dietitian can still recommend a vegetarian diet to the patient. BCAA concentrations are highest in vegetable and dairy products thus increasing the amount of BCAA in the patients diet overall.

Grade II