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"Role of oral supplementation of branched chain amino acids in the outcome of compensated alcoholic cirrhosis of liver."

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Abstract
Background:*Protein and energy deficiency is frequently seenin patients with alcoholic liver disease despite of taking adequate food as liverisresponsibleforthemetabolismofmanyhormonesthathave discordant effects on protein, carbohydrate, and lipid metabolism.In patients with advanced liver diseases serum concentrations of branched chain amino acids (BCAAs) are decreased, while the concentrations of aromatic amino acids (AAAs) phenylalanine and tyrosine are increased. Furthermore, a lower serum BCAA/aromatic amino-acid ratio is associated with aworse prognosis in patients with advanced liver disease including hepatic encephalopathy,edema,and ascites accompanied by hypoalbuminemia, insulin resistance, hepato-carcinogenesis, and infection caused by an impaired immune function.Hencethis study was undertaken to evaluatetheeffectoforalsupplementationofBCAAs in Compensated Alcoholic Cirrhosis ofLiver.*
Methods:*This cross-sectional study was conducted at Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from 2017 to 2019. 116 Compensated Alcoholic Liver Cirrhosis patients above 18 years of age who attended Gastroenterology OPD, Medicine OPD or admitted in the General Medicine wards were enrolled.Routine blood investigations baseline and after 3months of supplementation of oral BCAAs were done.*
Results: *The mean age of the patients was 40.06±7.95 years with majority of 83.1%males while 16.9% patients were females. Majority (81.1%) ofthem had historyofalcoholicintakedurationof<12 years.Patient'svariablesattheonsetofstudy(baseline)andattheendof3 months after supplementing with 6.3 grams of BCAApowder daily showed that there was statistically significant (p value <0.001) increase in Body mass index,improvement in liver function parameters and improvement in hepatic encephalopathy, Child Pugh score(CP), MELD score.*
Conclusions: *The presentstudy concluded that patient's clinical outcomes, liver function parameters and prognostic markers(CP score and MELD score) have improved significantly from baseline at the end of 3rd month of supplementation oral BCAAs. Branched chain amino acid supplementation has beneficial effecton prognostic markers in patients with advanced liver disease.*

Keywords*:Branched chain amino acid,Compensated Alcoholic Liver Cirrhosis, Child Pugh score, hepatic encephalopathy, MELD score*

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I. Introduction

Alcoholic liver disease or alcohol-related liver disease (ALD) is damage to the liver caused by excessive alcohol consumption, resulting in serious and life-threatening complications.In 2017, cirrhosis caused more than 1·32 million deaths (440000 in females and 883000 in males) globally .[1]ALD causes 47.9% of all liver cirrhosis deaths and 46.9% of all liver cirrhosis DALYs[2].The liver is responsible for the metabolism of many hormones that have discordant effects on protein, carbohydrate, and lipid metabolism, including insulin, the sex hormones, insulin-like growth factors, and glucagon. It is thus not surprising that chronic and acute liver disease can profoundly alter nutritional status and amino acid metabolism.[3]The branched-chain amino acids (BCAAs), valine, leucine, and isoleucine, are three of nine essential amino acids obtained from diet and not synthesized by our body. In patients with advanced liver diseases serum concentrations of BCAAs are decreased, while the concentrations of aromatic amino acids (AAAs) phenylalanine and tyrosine are increased.[4]The BCAAs serve not only as an essential substrate in the synthesis of body proteins, but also as an important regulator of protein turnover as well as maintenance of the body glutamate-glutamine level. Although

most of the amino acids are degraded in the liver, BCCAs are primarily catabolized by extra hepatic tissues (muscle, adipose, kidney, and brain)[5].BCAAs activate mTOR and subsequently increase the production of eukaryotic initiation factor 4E- binding protein-1 and ribosomal protein S6 kinase, which up regulate the synthesis of albumin.[4]

In the progression of liver cirrhosis, the depletion of BCCAs, such as leucine, isoleucine, and valine inhibit protein synthesis and protein turnover. Moreover, the skeletal muscle catabolizes BCAAs more rapidly than most other amino acids, and these increase the major complications of liver cirrhosis during disease progression: hepatic encephalopathy, edema, and ascites accompanied by hypoalbuminemia, insulin resistance, hepatocarcinogenesis, and infection caused by an impaired immune function.[6]

Protein and energy deficiency is frequently seen in ALD patients leading to hypoalbuminemia, inducing ascites and edema, where energy deficiency decrease fats, and muscle mass and causes muscle weakness, decreasing the quality of life of patients with liver cirrhosis[4].Furthermore, a lower serum BCAA/aromatic amino-acid ratio is associated with a worse prognosis in patients with advanced liver disease.[6] Several clinical trials from Western populations have suggested that oral BCAA supplementation significantly improved serum albumin concentration and health-related quality of life in patients with decompensated cirrhosis with an adequate daily food intake.[4]Therefore,this study is undertaken to evaluate the outcome of oral BCCAssupplementation in CompensatedAlcoholic Cirrhosis of Liver in south Asian subcontinent more specifically in subset of north-eastern Indian populations.

II. Materials and Methods

This cross-sectional study was conducted in Regional Institute of Medical Sciences (RIMS), Imphal, Manipur from September2017 to August 2019.116 Compensated Alcoholic Liver Cirrhosis patients who attended Gastroenterology OPD, Medicine OPD or admitted in the General Medicine wards were enrolled following the criteria.

Inclusion Criteria: Patients who were18years of age and above, giving consent for the study and diagnosedwith Compensated Alcoholic Liver Cirrhosis were included in the study.

Exclusion criteria included patients with other pre-existing liver conditions such as Hepatitis B, Hepatitis C, Autoimmune hepatitis, Non-alcoholic fatty liver, Biliary cirrhosis, drug induced liver diseases that may alter hepatic functions and those infected with HIV infected,those having chronic Diarrhoea, those on any protein supplements patients of Chronic Kidney Disease, Nephrotic Syndrome, those on anti-tubercular drugs and thosenot giving consent.

Study variables included independent variables like Complete Hemogram(CBC), Liver function test(LFT), Kidney function test(KFT), Prothrombin time and INR (PTINR),Ultrasound whole abdomen(USG), serum Lipid profile, Serology (HbsAg, Anti HCV Ab, HIV 1&2),ANA If indicated, Chest X ray, Mid Arm Circumference(MAC), skin fold thickness(SFT), body mass index (BMI). Upper GI Endoscopy, CT Abdomen were done as when required.

Outcome variables includedserum albumin, serum total bilirubin, INR, serum creatinine, MELD score and Child Pugh score

Procedures: Personal details including a detailed history of presenting symptoms, past history and personal history were recorded in proper proforma along with age, sex, body mass index (BMI), family history and duration of alcohol use. A detailed relevant clinical examination of every subject was also done including MAC, SFT and BMI were recorded. Patients were instructed to take 1 sachet of branched chain amino acid (6 g per sachet containing L-leucine - 2760 mg, isoleucine -1920 mg and valine- 1656 mg) dissolved in 100 ml of water before bed time daily for 3 months. With the participants consent, blood samples were collected for serum albumin, total bilirubin, INR and other routine investigations at the beginning of study and end of 3 month.

Study tools:

- Serum Albumin reflect the synthetic dysfunction of liver. Normal serum albumin level ranges from 3.5- 5.5 g/dL. Hypoalbuminemia was diagnosed if serum albumin level < 3.5 g/dL.[7] Liver Function test was done by enzymatic analyser.

- International normalized ratio (INR) expresses the degree of hepatic anticoagulation. PTINR was done by Haemostatics analyser (thromboplastin reagent was used.) Normal range INR: 0.9 -1.2.[7]
- Serum bilirubin is a measure of hepatic conjugation and excretion. Normal ranges between 0.1- 1 mg/dL.[7]
- Child Pugh classification of cirrhosis was used to assess the prognosis in liver cirrhosis.
- **Interpretation:** score ranges from 5 to 15
  - Class A: score between 5-6 (compensated)
  - Class B: score between 7 -9 (decompensated)

- Class C: score between ≥10 (decompensated)

Modified End-Stage Liver disease (MELD) score was used to assess the severity in liver cirrhosis [7] by using the MELD calculator.

Other routine investigations like CBC was done by Haematology automated analyser. Kidney function test used Kinetic method for serum urea and Jaffe's method for creatinine. Blood sugar was done by GOD/PAP method. Serum Lipid profile was done by RaniboxXimolaautoanalyzer. Serology like Hepatitis B was done by Virucheck method, Hepatitis C by Flavi screen method and HIV 1 & 2 by Rapid test. Mid-Arm Circumference was measured by tape, skin fold thickness was measured by Calliper and BMI.

Statistical analysis: Data were analysed using statistical package for social sciences version 21. Descriptive statistics like mean, standard deviation, percentages and student t test (two tailed, dependent) were used to find the significance of study parameters on continuous scale. Significance was assessed at 5 % level of significance and a P value of <0.05 was considered significant.

Approval of Research Ethics Board and Informed consent: The study was approved by Research Ethics Board Regional Institute of Medical Sciences, Imphal.(No. A/206/REB-Comm (SP)/RIMS/2015/415/33/2018).

III. Results

A total of 116 patients with Compensated Alcoholic Liver Cirrhosis above 18 years of age were included in the study. The mean age of the participants was 40.06±7.95 years and majority of the participants (43.2%) were in the age group of 31-40years. Majority (83.1%) of the participants were males while 16.9% werefemales.The mean BMI was 23.07±2.84 (Table 1).Majorityofpatientspresentedwithabdominaldiscomfort(14.4%),anorexia(14.4%)andnausea(14.4%)followed by vomiting(11.9%),pain abdomen(11%),fatigue(11%),decreasesleep(9.3%),irritability(8.5%)and hiccup (5.1%)(Figure1).Majorityofpatients81.1%had historyofalcoholintakedurationof< 12 years and 18.6 % of them had >12 yearsduration (Table2). At baseline, no significantdifferencewasnotedinage,sex,gender,occupation, alcohol intake duration, symptoms, MAC, TSFT,serum bilirubin, albumin AST, ALT, INR, hemoglobin level, platelet count, CPscore and MELD score. CP Score and MELD score were on higher side at thebaseline. Patient'svariablesattheonsetofstudy(baseline)andattheendof3 months after supplementing with 6.3 grams of branched chain amino acidpowder dailyshowed that there was statistically significant (p value <0.001) increase in MAC,TSFT,BMI and improvement in the levels of total bilirubin, liver enzymes, serum albumin, PTINR, serum creatinine and platelet count (p value <0.001) (Table3).There was improvement in hepatic encephalopathy , CP score, MELD score after 3 months of supplementation of oral BCAAs (Figure 2.3.4).

Table 1: Baseline characteristics of BCAA's treated patients(N=118).

Characteristics	Baseline
Number ofpatients	118
Age, years, mean ±SD	40.06±7.95
Male/Female, n,%	98 (83.1 %)/ 20(16.90%)
MAC (cm), mean ±SD	30.78±1.89
Triceps Skinfold thickness(mm)	23.37±4.13
BMI, Kg/m^2, mean ±SD	23.07±2.84
Total Bilirubin (mg/dL), mean ±SD	1.33±0.42
S. Albumin (g/dL), mean ±SD	3.81±0.17
AST (IU), mean ±SD	107.27±16.65
ALT (IU), mean ±SD	79.11±14.78
INR, mean ±SD	1.41±0.20
S. Creatinine (mg/dL), mean ±SD	0.91±0.25
Hemoglobin (g/L), mean ±SD	11.82±1.00
Platelet ($x10^9$/L), mean ±SD	213.93±34.96
Ascites (none/mild/moderate-severe),n	111/7/0
HepaticEncephalopathy (none/Grade 1-2/Grade 3-4),n	118/-/-
MELD Score, mean ±SD	11.51±2.85
CP SCORE	5.35±0.48

Figure1: Symptoms wise distribution of the patients.

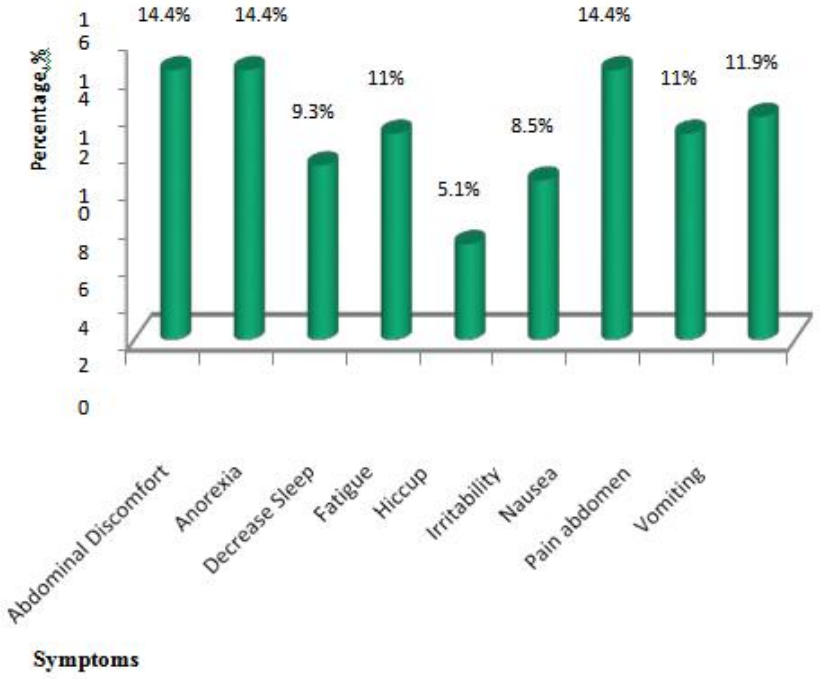


Table 2: Duration of Alcohol distribution of patientsstudied.

Duration ofAlcohol(years)	No. ofpatients	%
≤12	96	81.4
>12	22	18.6
Total	118	100.0

Table 3.Characteristics at baseline and the end of 3 months of supplementation of oral BCAAs

variables	Baseline	3months	difference	t value	P value
MAC(cm)	30.78±1.89	31.15±1.83	-0.367	-15.639	0.001
TricepsSkinfold thickness(mm)	23.37±4.13	25.33±4.18	-1.958	-14.354	0.001
BMI(Kg/m^2)	23.07±2.84	23.45±2.84	-0.378	-27.014	0.001
TotalBilirubin (mg/dL)	1.33±0.42	0.83±0.26	0.497	19.627	0.001
S. Albumin (g/dL)	3.81±0.17	4.12±0.23	-0.308	-34.074	0.001
AST(IU)	107.27±16.65	36.86±4.87	70.407	56.019	0.001
ALT(IU)	79.11±14.78	30.03±3.81	49.076	41.441	0.001
INR	1.41±0.20	1.07±0.13	0.336	24.837	0.001
S.Creatinine (mg/dL)	0.91±0.25	0.72±0.18	0.184	15.516	0.001
Hemoglobin (g/L)	11.82±1.00	13.2±0.83	-1.383	-26.472	0.001
Platelet($x10^9/L$)	213.93±34.96	247.42±37.24	-33.483	-28.756	0.001
MELDScore	11.51±2.85	7.21±1.45	4.297	22.886	0.001
CP SCORE	5.35±0.48	5.00±0.00	0.35	7.893	0.001

Figure2:HepaticEncephalopathydistributionofstudypopulationat Baseline and end of3 months afterdaily oral intakeof6.3 g ofBCAA's.(N= 118)

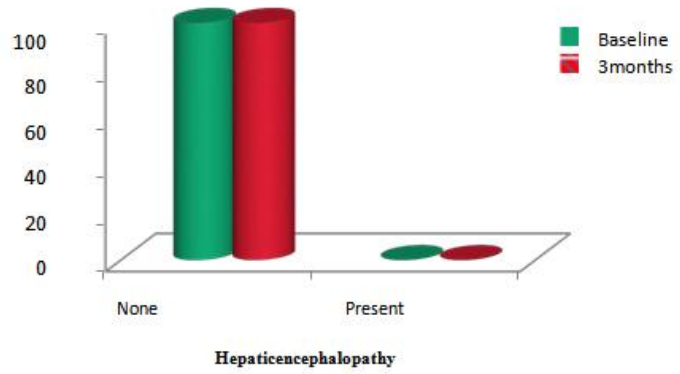


Figure 3: CPscoredistributionbetweenmaleandfemalepatientson6.3g BCAA's at Baselineand end of3 months. (N=118)

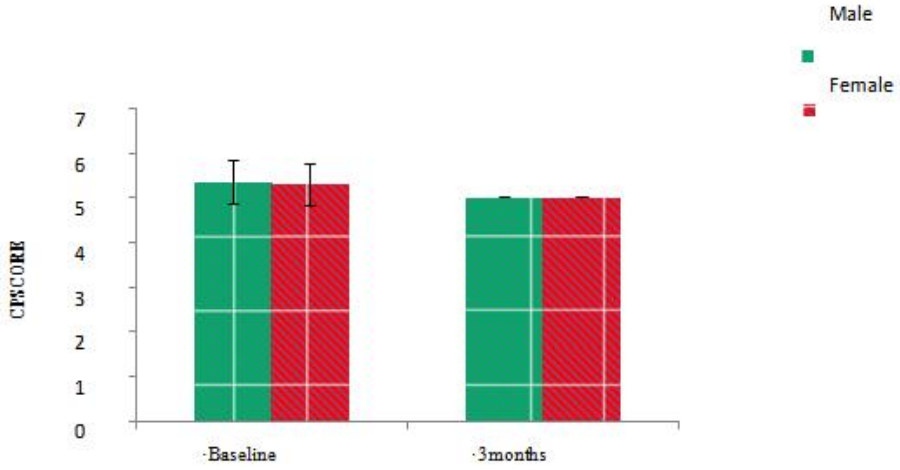
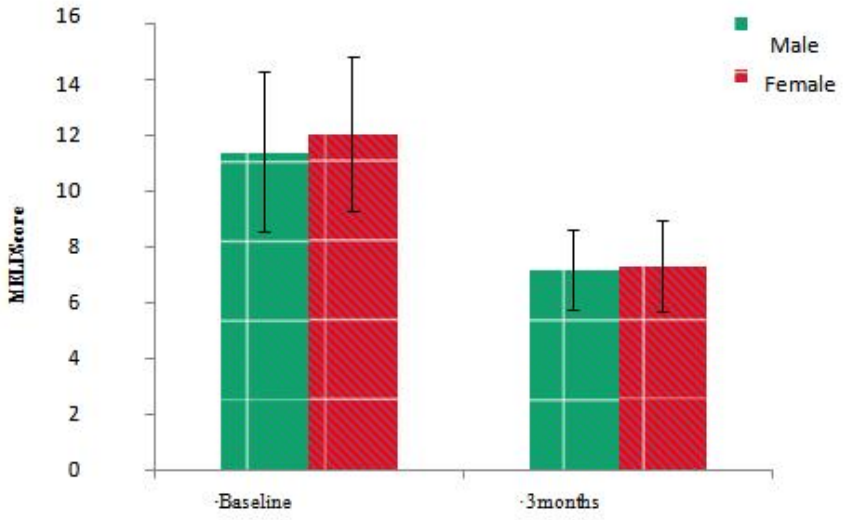


Figure 4: MELD score distribution of study population between male andfemale patients on 6.3 gBCAA's atBaselineand end of3 months



IV. Discussion

In Alcoholic liver disease, the progression of chronic liver disease isassociated with the metabolism of amino acids resulting in a decreasedcirculating BCAA/aromatic amino-acid ratio.[8,9]Early studies on the effectivenessof BCAA supplementation in patients with chronic liver disease focusedon malnutrition and encephalopathy.[10,11]Two large-scale randomized controlled trials showed that deterioration of liver disease andits complicationswithorwithoutthedevelopmentofHCC,improvedduringoral BCAAsupplementation.[12,13]Thebaselineparametersofourstudyaresimilarto the multicenter, retrospective, observational cohort study of Park GJ et al[6]Bianchi G et al[12] in his study showed MAC and TSFT increased significantly (p-value <0.05) upon supplementation with 14.4 gof BCAA'sdailyfor12monthsin advanced liver disease.MaharshiSetal[14]also concluded statistically significant(p-value <0.01) increased in MAC, TSFT upon supplementationwith12.5gramsofBCAA'sfor6 months. These studies are comparable to our study where our patientswere supplement with 6.3 g of oral intake of BCAA's powder daily for 3 months following which therewassignificant(P value =0.001) increaseinMAC from 30.78±1.89 cm to 31.15±1.83 cmand TSFT, from 23.37±4.13 to 25.33±4.18. In a multicenter,randomizedcontrolledtrial by MutoYetal[13]studiedasupplementationwith12goforalBCAA'sdailyfor2years in advanced liver disease, the obesityratewas28%(BMI>25kg/m^2). However,inthepresentstudythere is slight increase in BMIfrom 23.07±2.84 to 23.45±2.84, which is statisticallysignificant (p-value = 0.001).ParkGJetal[6] in his study of 166 patients weresupplemented with12.45gofBCCA'sdailyfor6months reported thatBCAA's treatedgroup,theserumbilirubinlevel,serumalbuminlevel, CPscore and MELD score improved significantly(P <0.05)over time while there were no significant changes in these parameters in the non-BCAA's groups. Similar results were concluded by Bianchi G et al[12] and Kawaguchi T et al[15]. These results were comparable with the study, serum bilirubin level improved from 1.33±0.42to 0.83±0.26 mg/dL; p-value = 0.001, serum albumin from 3.81±0.17 to 4.12±0.23 g/dL; P value = 0.001. In the BCAA'streatedgroup the serum albumin level (p-value = 0.067), serum bilirubin level (p-value= 0.0012), prothrombin time and INR improved significantly(p-value = 0.001from 1.41±0.20 to 1.07±0.13). CP scoreimproved significantlystatistically(p-value=0.0001) from9.1±0.3to7.9±0.3.

In Park GJ et al[6]in his study of 166 patients supplemented with12.45gofBCCA'sdailyfor6months notedno significant difference in the serum creatinine level (p-value = 0.515) which differed from our present where there was statistically significant improvement (p-value= 0.001). Kawaguchi T et al[15]studied 85 patients supplemented with 12 g of BCAA's granules for 12 months and found significantimprovement in Hb level and platelet counts which was similar to our study (p -value = 0.001).

Bianchi G et al[12] in his study concluded that theprevalenceofasciteswasreduced whilethere were no significant differences inencephalopathyscore.But CP score improved significantly (p- value < 0.00001) from 9.1 ± 0.3 to 7.9 ± 0.3. These findings are comparable to our study where at the end of 3 months, there were noascitesand also no significantdifferencesinhepaticencephalopathy while CP score improved significantly (p-value=0.001) from baseline 5.35±0.48to 5.00±0.00. Park GJetal[6] studiedtheeffectsofBCAA on the MELD score and found statistically significant improvement (p-value= 0.004) after 6 months of BCAAs.Similarly, in our study,MELDscore improved significantly (p-value=0.001)frombaseline11.51±2.85to7.21±1.45.

V. Conclusion

Branched chain amino acid supplementation has beneficial effecton prognostic markers in patients with advanced liver disease. In the presentstudy patient's clinical outcomes, liver function parameters and prognostic markers(CPscore and MELD score) have improved significantly from baseline at the end of3rdmonth of supplementation oral BCAAs.However, the optimum doseof BCCAsupplied in variousstudies is variable and dose findings studies are needed to optimum dosage,safe limits of administration andwhether higher dose will produce better results.A further long-term prospective study would be needed to delineatethe efficacy of oral BCAAs and overcome theselimitations.

Declarations:
Funding: None
Conflict of Interest: None declared
Approval of research ethics board**:** Taken

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