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IMPACT OF HEPAPRO PROTEIN SUPPLEMENTATION ON CLINICAL RECOVERY IN PATIENTS WITH LIVER DISEASE: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Protein-energy malnutrition is a common complication of liver diseases, contributing to impaired hepatic function, systemic inflammation, sarcopenia, and poor quality of life.

Methods: This prospective controlled study evaluated the effects of HepaPro protein supplementation (enriched with BCAA, SAMe) on liver function, nutritional status, inflammatory biomarkers, lipid profile, anthropometric parameters, fatigue, appetite, and quality of life in 40 patients with liver cirrhosis and 20 healthy controls. Cirrhotic patients received 30 g of protein supplement twice daily for 8 weeks, and biochemical, anthropometric, and clinical parameters were assessed before and after intervention.

Results: Protein supplementation significantly improved liver function and nutritional status, with SGOT decreasing from 148.8 to 103.9 U/L (30.2%), SGPT from 104.3 to 73.6 U/L (29.4%), bilirubin from 2.86 to 1.71 mg/dL (40.3%), and CRP from 15.30 to 6.99 mg/L (54.3%) ($p < 0.01$ for all). Significant increases were observed in albumin (3.02–3.71 g/dL; 22.9%), total protein (6.16–6.86 g/dL; 11.4%), and the albumin-to-globulin ratio (0.82–1.02; 24.0%) ($p < 0.001$). Lipid metabolism improved with normalization of total cholesterol, LDL cholesterol, and triglyceride levels, accompanied by significant improvements in body mass index, triceps skinfold thickness, fatigue severity, appetite, and Chronic Liver Disease Questionnaire scores ($p < 0.001$). In contrast, the placebo group exhibited no significant changes in liver enzymes, bilirubin, inflammatory markers, lipid profile, or anthropometric measurements. No adverse effects were observed among health controls. **Conclusion:** These findings demonstrate that HepaPro protein supplementation is an effective adjunctive medical nutritional intervention that significantly improves hepatic function, nutritional status, inflammatory profile, metabolic parameters, and patient-reported outcomes in individuals with liver cirrhosis and acute liver diseases.

KEYWORDS: Liver diseases, Protein supplement, BCAA, RCT, Intervention study.

INTRODUCTION

Chronic and Acute liver diseases and cirrhosis represent major causes of morbidity and mortality worldwide and are associated with significant metabolic and nutritional disturbances (1,2). As liver disease progresses, patients frequently develop protein-energy malnutrition, which affects approximately 50–90% of individuals with advanced cirrhosis and contributes to poor clinical outcomes, increased susceptibility to infections, prolonged hospitalization, and reduced survival (3–5). Malnutrition in hepatic disorders arises from multiple factors, including reduced dietary intake, impaired nutrient absorption, altered substrate metabolism, hypermetabolism, and diminished hepatic synthetic function (2,5).

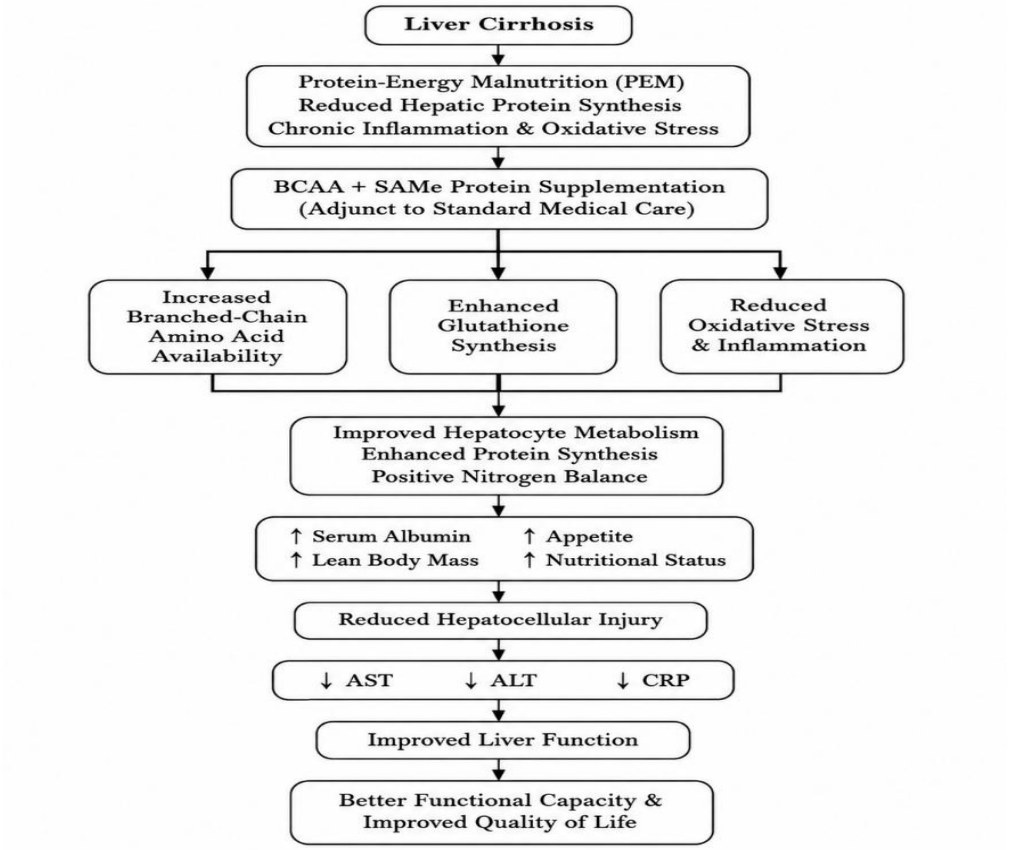
Protein metabolism is profoundly affected by patients with chronic liver disease. Reduced hepatic protein synthesis results in hypoalbuminemia, negative nitrogen balance, and progressive loss of skeletal muscle mass, leading to sarcopenia and functional impairment (6,7). Sarcopenia has emerged as an independent predictor of mortality, hepatic decompensation, and poor quality of life in patients with cirrhosis (8,9). Furthermore, deterioration in nutritional status is often accompanied by alterations in anthropometric measurements such as body weight, body mass index (BMI), and triceps skinfold thickness (TSF), as well as biochemical abnormalities including decreased serum albumin and total protein concentrations (3,6).

Current nutritional guidelines emphasize the importance of adequate protein intake in patients with chronic liver disease and discourage unnecessary protein restriction, even in those with hepatic encephalopathy (1,2,10). Increasing evidence suggests that protein supplementation can improve nitrogen balance, preserve lean body mass, enhance serum protein synthesis, and support overall nutritional recovery (2,10). Supplementation with high-quality protein and branched-chain amino acids has also been associated with improvements in muscle metabolism, nutritional status, and clinical outcomes in patients with cirrhosis (11,13).

In addition to improving nutritional status, dietary protein supplementation may positively influence liver function and systemic inflammation. Previous studies have demonstrated associations between nutritional interventions and improvements in serum albumin, total protein, aminotransferases, bilirubin levels, and inflammatory biomarkers such as C-reactive protein (CRP) (2,5,11). These biochemical and anthropometric indicators are widely used to assess disease severity, nutritional status, and therapeutic response in patients with hepatic disorders (3,13).

Despite growing recognition of the role of nutrition in liver disease management, real-world evidence evaluating the effectiveness of structured protein supplementation programs remains limited, particularly among patients with varying degrees of hepatic dysfunction. Evaluating the impact of structured protein supplementation in routine clinical settings is essential for establishing its role as an adjunct therapeutic strategy and for optimizing patient care. Moreover, assessment of changes in anthropometric, biochemical, and inflammatory parameters can provide valuable insights into the efficacy of nutritional interventions across varying stages of disease severity.

Therefore, this randomized controlled trial (RCT) was designed to investigate the efficacy of protein supplementation as an adjunctive medical nutritional intervention in patients with chronic liver disease. Specifically, the study evaluated its effects on anthropometric and biochemical indicators of nutritional status, liver function tests, lipid profile, inflammatory biomarkers, and patient-reported clinical outcomes to determine its potential role in improving overall disease prognosis and quality of life.



Proposed mechanism of action of BCAA and SAMe protein supplementation in patients with liver cirrhosis. Branched-chain amino acid (BCAA) and S-adenosyl-L-methionine (SAMe) supplementation enhances protein synthesis, improves nitrogen balance, increases glutathione production, and reduces oxidative stress and inflammation. These effects improve hepatocyte function, resulting in increased serum albumin concentrations, reduced liver injury markers (AST and ALT), decreased systemic inflammation (CRP), improved nutritional status and appetite, and ultimately better liver function and quality of life.

MATERIALS AND METHODS

Study population

Forty patients who were diagnosed of having liver cirrhosis based on clinical and histological evidence, or imaging diagnosis, were recruited from local hospital from Mysuru and Bengaluru. Exclusion criteria included the following: having renal failure, malignancies, diabetes mellitus, infectious diseases, cardiac disease, acquired immune deficiency syndrome, pancreatic insufficiency and being pregnant or lactating. The severity of liver cirrhosis was graded using **Child-Pugh scores**. Informed consent was obtained from all participants prior to enrollment.

A total of 60 participants were enrolled in the study and randomized into three groups: Control (n = 20), Placebo (n = 20), and Test (n = 20).

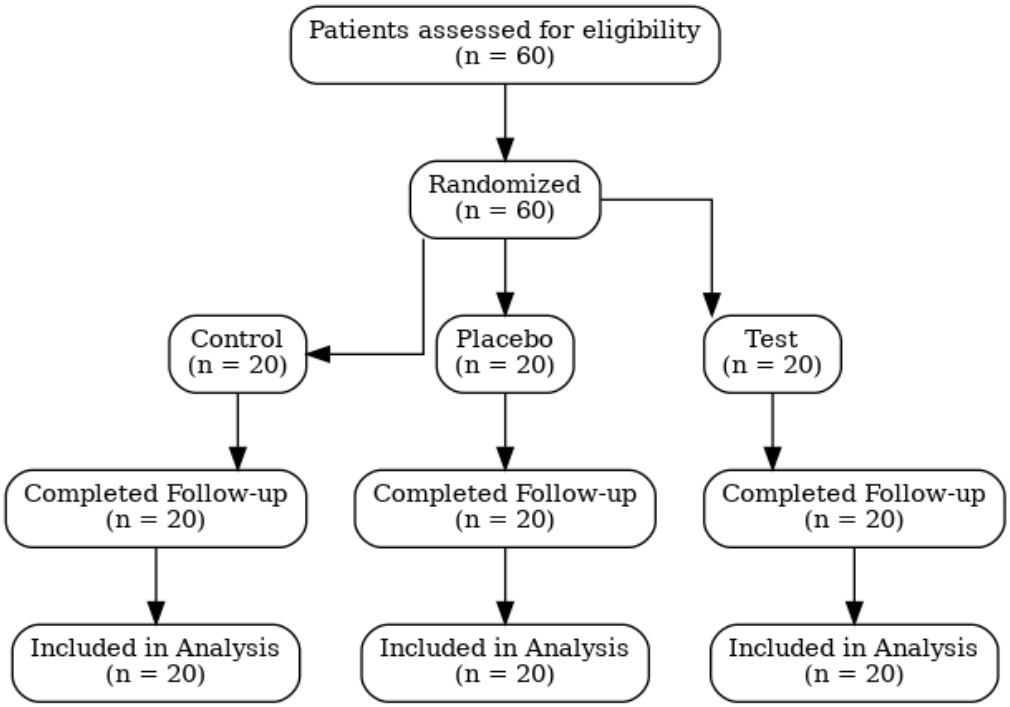
Eligibility Criteria for Participant Selection

Inclusion Criteria	Exclusion Criteria
Age ≥**18** years	**Renal failure** or chronic kidney disease requiring medical intervention
Male and female participants	Presence of any **malignancy** (cancer)
Adults diagnosed with liver cirrhosis based on clinical findings, histopathological evidence, or imaging diagnosis	**Diabetes mellitus** with pancreatic insufficiency
Patients recruited from **tertiary care hospitals** in Mysuru and Bengaluru	**Active infectious diseases**
Patients classified according to the **Child–Pugh scoring system** for assessment of liver cirrhosis severity	Significant **cardiac** disease
Patients willing to participate and who provided written **informed consent**	**Human Immunodeficiency Virus** (HIV) infection/acquired immunodeficiency syndrome (AIDS)
Patients able to comply with the study **protocol and intervention**	**Pregnant or lactating women**
	Patients unwilling or **unable** to provide written **informed consent**

Study design

Sample size justification: A convenience sampling method was adopted for this hospital-based cross-sectional study. All consecutive eligible patients with liver disease attending the participating tertiary care hospitals during the study period who met the inclusion criteria were invited to participate. A total of 60 participants were recruited within the study period.

The study was conducted for 8 weeks of intervention. Each tested group was given 30g of protein supplementation in 150ml of water twice day. The supplementation was given along with their normal diet and medications. Below table explains the supplementation composition in detail.



Participant Flow Through the Study

Nutrition per pack of supplement

Nutrients	Test sample Values per 100g	Placebo sample Values per 100g
Energy (Kcal)	401kcal	403kcal
Protein (g)	25g	2g
Carbohydrate (g)	55g	84g
Fat (g)	9g	7g

Calcium (mg)	380mg		60mg
Sodium (mg)	140mg		142mg
Potassium (mg)	370		280mg
Enriched	**BCAA (Branched chain amino acids)**	**15g**	Nil
	Lysine	**2.5g**	
	SAMe (S-adenosylmethionine)	**200mg**	
	Omega	**1300mg**	
	ALA (Alpha-Linolenic Acid)	**200mg**	
	Taurine	**88mg**	
	LOLA (L-ornithine-L-aspartate)	**3g**	
	Carnitine	**50mg**	

Intervention: A 30 g serving of the protein supplement was reconstituted by mixing with 50 mL of lukewarm water to obtain a smooth slurry. Lukewarm water was subsequently added to make up a final volume of 150 mL, and the preparation was stirred until uniformly dispersed. Test group patients (n=20) were given the supplement twice daily for 8 consecutive weeks, whereas placebo group patients were given nutritional formula for 8 consecutive weeks.

Nutritional Interventions Administered to the Study Groups

Group	Intervention
Control	Standard dietary management/standard of care only
Placebo	Standard dietary management + placebo supplement
Test	Standard dietary management + liver-specific nutritional supplement (high protein + BCAA + SAMe)

Assessment of anthropometric measurements (14): Body weight and Triceps Skinfold Thickness were measured by trained personnel following standardized procedures.

Body weight (kg) was measured using a calibrated digital weighing scale with participants wearing light clothing and no footwear. Measurements were recorded to the nearest 0.1 kg.

Body Mass Index (BMI) was calculated using the following formula:

$BMI = Weight\ (kg)/Height^2\ (m^2)$

BMI values were expressed in kg/m^2 and categorized according to the World Health Organization (WHO) classification criteria.

Triceps Skinfold Thickness (TSF) was measured using a calibrated skinfold calliper (e.g., Harpenden or Lange skinfold calliper). The measurement was taken at the midpoint between the acromion process of the scapula and the olecranon process of the ulna on the non-dominant arm. The skinfold was gently grasped and measured in triplicate, and the average value was recorded in millimetres (mm). TSF was used as an indicator of subcutaneous fat stores and nutritional reserves.

Assessment of blood biomarkers measurements (15)

Venous blood samples were collected from all participants at baseline and after 8 weeks of protein supplementation following an overnight fast of 10–12 hours. Approximately 5–10 mL of blood was drawn by venipuncture under aseptic conditions and distributed into plain and EDTA-coated vacutainer tubes for biochemical analyses. Serum was separated by centrifugation at 3,000 rpm for 10 minutes and stored at −20°C until further analysis.

Liver functional test: serum glutamate oxaloacetate transaminase (SGOT/AST), serum glutamate pyruvate transaminase (SGPT/ALT), total bilirubin, total protein, and serum albumin, were analysed using commercially available diagnostic kits according to the manufacturer's instructions on a fully automated clinical chemistry analyser.

Lipid profile parameters: including total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides, were determined enzymatically using standard commercial assay kits and measured on an automated biochemistry analyser. Results were expressed in mg/dL.

C-reactive protein (CRP): a marker of systemic inflammation, was quantified using a high sensitivity immunoturbidimetric assay according to the manufacturer's protocol and expressed as mg/L.

Assessment of Quality of Life & Functional Outcomes (16)

Quality of life (QoL) and functional outcomes were assessed at baseline and after 8 weeks of protein supplementation using validated patient-reported outcome measures. These assessments were performed to

evaluate the impact of nutritional intervention on physical functioning, fatigue, appetite, and overall well-being in patients with hepatic cirrhosis.

Fatigue Severity Scale (FSS): Fatigue was assessed using the Fatigue Severity Scale, a validated 9-item questionnaire designed to evaluate the impact of fatigue on daily activities and quality of life. Each item was scored on a 7-point Likert scale ranging from 1 (strongly disagree) to 7 (strongly agree). The final FSS score was calculated as the means of all item scores, with higher scores indicating greater fatigue severity. A reduction in FSS score following intervention was considered indicative of improvement in fatigue-related symptoms.

Simplified Nutritional Appetite Questionnaire (SNAQ): Appetite and nutritional intake were evaluated using the Simplified Nutritional Appetite Questionnaire. The questionnaire consists of four items assessing appetite, satiety, food taste, and meal frequency. Total scores range from 4 to 20, with higher scores reflecting better appetite and nutritional intake. An increase in SNAQ score following supplementation was interpreted as an improvement in appetite and dietary behavior.

Chronic Liver Disease Questionnaire (CLDQ): Disease-specific quality of life was assessed using the Chronic Liver Disease Questionnaire, a validated instrument specifically developed for patients with chronic liver diseases. The CLDQ comprises 29 items distributed across six domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, and worry. Responses are recorded on a 7-point Likert scale, where higher scores indicate better quality of life. The overall CLDQ score was calculated as the mean of all domain scores.

Participants completed all questionnaires under the supervision of trained investigators to ensure completeness and accuracy. The assessments were conducted in the participants' preferred language whenever validated translations were available. Changes in FSS, SNAQ, and CLDQ scores between baseline and post-intervention were used to determine the effects of protein supplementation on functional capacity, appetite, fatigue, and health-related quality of life.

Parameter	Assessment Tool	Score Range
Fatigue	Fatigue Severity Scale (FSS)	1–7
Appetite	Simplified Nutritional Appetite Questionnaire (SNAQ)	4–20
Quality of Life	Chronic Liver Disease Questionnaire (CLDQ)	1–7

Clinical and demographic data

Variables	All patients
Sex (M/F)	28/14
Age	55.93 ± 1.914
Child-Pugh Classification, n	
Child A	11
Child B	19
Child C	10
Etiology of the liver cirrhosis	
Alcohol	21
Virus	16
Other	3
Career	
White collar job	33
Blue collar job	1
Unemployed	6
Controls samples	
Sex (M/F)	13/7
Age	51.7 ± 14.2

Statistical analysis

For statistical analysis graph pad prism 8.0 has been used. One way ANNOVA is applied for multiple group comparison. And the data represented in mean ± SEM values of 20 samples in each group.

RESULTS

Parameter	Supplementation group (test) [n=20]		Placebo control [n=20]		Control samples [n=20]		Normal range
	Baseline (Mean ± SEM)	Post Intervention (Mean ± SEM)	Baseline (Mean ± SEM)	Post Intervention (Mean ± SEM)	Baseline (Mean ± SEM)	Post Intervention (Mean ± SEM)	
SGOT (AST) U/L	148.8 ± 11.29	103.9± 7.5	240 ± 12.97	242 ± 10.55	27.95±0.7897	26.2 ± 0.7595	10–40
SGPT (ALT) U/L	104.3 ± 7.123	73.6 ± 4.712	155 ± 7.048	157 ± 8.6	25 ± 0.8111	23 ± 0.7071	7-56
<BMI (kg/m²)	22.82 ± 0.2614	24.10 ± 0.2550	23.21 ± 0.3837	25.4 ± 0.6	23.84 ± 0.2449	24.67 ± 0.2484	18.5 -24.9
Body Weight (kg)	64.90 ± 1.544	68.75 ± 1.605	69.7 ± 2.098	71.33 ± 3.22	69.05 ± 2.059	72 ± 2.076	-
A/G Ratio	0.8215 ± 0.035	1.019±0.0275	0.5835 ± 0.028	0.79 ± 0.03	1.431 ± 0.007743	1.512 ± 0.008	1.0-2.2
Total Protein (g/dL)	6.160 ± 0.1417	6.860±0.079	5.125 ± 0.1390	7.64 ± 0.22	7.305 ± 0.02945	7.805 ± 0.02945	6.0-8.3
Total Bilirubin (mg/dL)	2.855 ± 0.2989	1.705 ± 0.1787	5.355 ± 0.3653	6.25 ± 0.6	0.81 ± 0.02705	0.71 ± 0.02705	0.2-1.2
Serum Albumin (g/dL)	3.015 ± 0.1306	3.705± 0.094	2.080 ± 0.1224	3.22 ± 0.32	4.435 ± 0.015	4.785 ± 0.015	3.5-5.0
Triceps skinfold thickness (mm)	13.65 ± 0.6419	16.15±0.5442	9.5 ± 0.4947	10.65 ± 0.66	16.2 ± 0.4899	18.2 ± 0.4899	M-8-20; F-15-30
Total Cholesterol (mg/dL)	143.6 ± 4.475	162.8±3.792	114.1 ± 3.283	116.5 ± 4.6	181.3 ±1.476	187.3 ± 1.476	< 200
LDL (mg/dL)	77.7 ± 2.660	90.40±2.297	60.85 ± 1.829	62.21 ± 2.2	100.9 ±1.244	104.9 ± 1.197	< 100
Triglycerides (mg/dL)	133.5 ± 2.419	125.6±2.208	152 ± 2.531	154 ± 3.1	125.2 ±1.527	121.8 ± 1.41	< 150
CRP (mg/L)	15.3 ± 1.816	6.985 ±0.5913	19.42 ± 1.297	21.22 ± 2.3	1.64 ± 0.08442	1.255 ± 0.07521	< 10
FSS	6.218±0.07424	4.163±0.065(32.8%)			NA	NA	1-7
SNAQ	9.55±0.2581	13.88±2353 (40.7%)			NA	NA	4-20
CLDQ	3.853±0.05064	5.275±0.05613 (42.1			NA	NA	1-7

Effect of protein supplementation on liver function and inflammation

The effect of protein supplementation on biochemical and nutritional parameters in patients with hepatic cirrhosis is presented in Figure 1. A significant improvement was observed in liver function markers, protein status, inflammatory indices, and nutritional parameters following the intervention period.

Serum aminotransferase levels showed a marked reduction following protein supplementation. The mean SGOT (AST) concentration decreased from 148.8 U/L at baseline to 103.9 U/L post-supplementation, representing a reduction of approximately 30.2% ($p = 0.0020$). Similarly, SGPT (ALT) levels declined significantly from 104.3U/L to 73.6U/L, corresponding to a reduction of approximately 29.4% ($p = 0.0009$). These findings indicate improved hepatocellular integrity and reduced ongoing liver injury following nutritional intervention.

A significant improvement in hepatic excretory function was also observed. Mean serum bilirubin levels decreased from 2.86 mg/dL at baseline to 1.71 mg/dL after supplementation, representing a reduction of approximately 40.3% ($p = 0.0021$). This decline suggests enhanced bilirubin clearance and recovery of liver function. Concurrently, serum albumin concentrations increased significantly from 3.02 g/dL to 3.71 g/dL, corresponding to an increase of approximately 22.9% ($p = 0.0001$), reflecting improved hepatic synthetic capacity and better nutritional status.

Nutritional biomarkers demonstrated further improvement following supplementation. Mean total protein levels increased from 6.16 g/dL to 6.86 g/dL, representing an increase of approximately 11.4% ($p = 0.0001$), indicating restoration of circulating protein levels and enhanced protein metabolism. Likewise, the albumin-to-globulin (A/G) ratio improved significantly from 0.82 to 1.02, corresponding to an increase of approximately 24.0% ($p < 0.0001$). The normalization of the A/G ratio suggests improved hepatic protein synthesis and restoration of protein homeostasis.

Systemic inflammation was markedly attenuated after supplementation, as evidenced by a significant reduction in C-reactive protein (CRP) levels. Mean CRP concentrations decreased from 15.30 mg/L at baseline to 6.99 mg/L post-supplementation, representing a reduction of approximately 54.3% ($p < 0.0001$). This substantial decline indicates a significant reduction in systemic inflammatory burden in cirrhotic patients following protein supplementation.

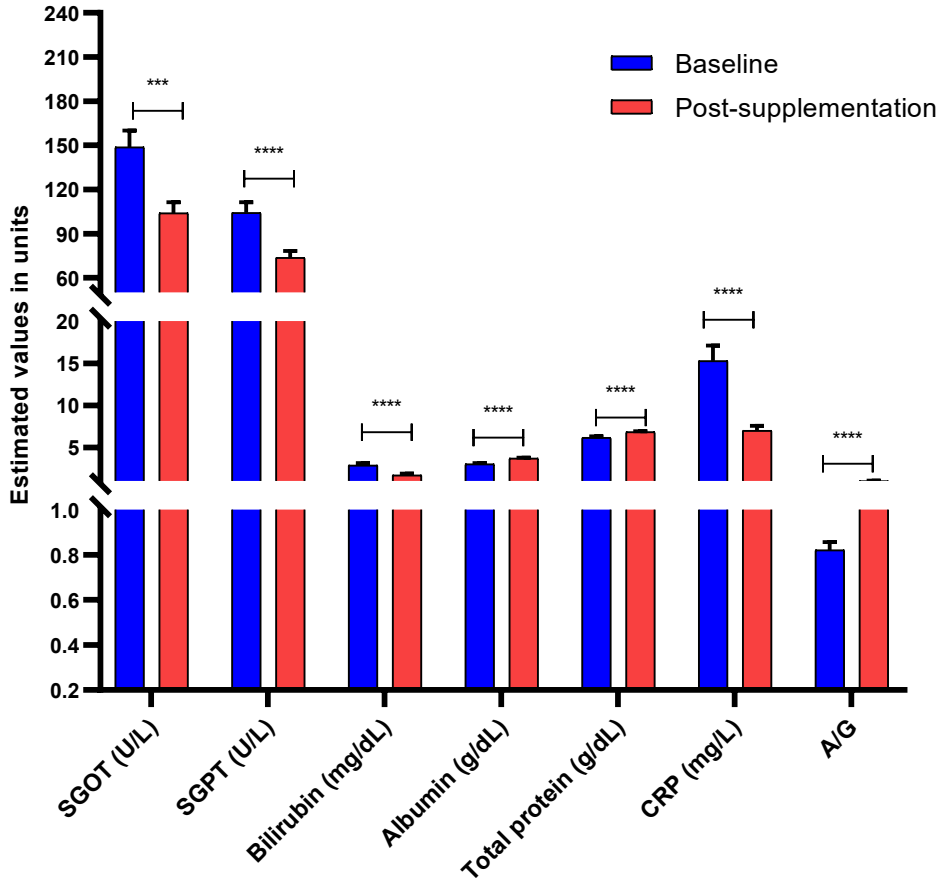


Figure 1: Effect of protein supplementation on biochemical parameters in patients with hepatic cirrhosis. Data are presented as mean ± SEM. Protein supplementation significantly reduced SGOT, SGPT, total bilirubin, and CRP levels while significantly increasing serum albumin, total protein, and A/G ratio compared with baseline values. Statistical significance was determined using a paired t-test. ****p < 0.0001 versus baseline.

TABLE 1: Statistical analysis for liver function and inflammation parameter on protein supplementation

	Significance	P value	Mean of Baseline	Mean of post-supplementation
SGOT (U/L)	Yes	0.002036	148.8	103.9
SGPT (U/L)	Yes	0.000900	104.3	73.60
Bilirubin (mg/dL)	Yes	0.002095	2.855	1.705
Albumin (g/dL)	Yes	0.000119	3.015	3.705
Total protein (g/dL)	Yes	0.000110	6.160	6.860
CRP (mg/L)	Yes	0.000097	15.30	6.985
A/G	Yes	0.000076	0.8215	1.019

In the placebo control group, serum aminotransferase levels remained largely unchanged throughout the study period. Mean SGOT (AST) and SGPT (ALT) values exhibited only minimal increases following the intervention period, and these differences were not statistically significant ($p > 0.05$). These findings indicate that the placebo intervention did not produce any measurable improvement in hepatocellular injury.

Similarly, serum bilirubin concentrations showed a slight increase compared with baseline; however, this change was not statistically significant ($p > 0.05$), suggesting that hepatic excretory function remained essentially unchanged during the study period. Markers of hepatic synthetic function demonstrated modest improvements. Serum albumin levels increased significantly following the intervention ($p < 0.01$), while total protein concentrations also showed a significant increase ($p < 0.001$). These changes may reflect routine clinical management, dietary variation, or the natural course of recovery rather than a specific treatment effect, as participants received placebo instead of protein supplementation.

Although C-reactive protein (CRP) levels showed a slight increase after the intervention, the difference was not statistically significant ($p > 0.05$), indicating that systemic inflammatory status remained largely unchanged in the placebo group.

A significant increase was also observed in the albumin-to-globulin (A/G) ratio ($p < 0.001$), suggesting a modest improvement in protein balance. However, the magnitude of this change was smaller than that observed in the protein-supplemented group and should be interpreted in the context of concurrent standard medical care and individual biological variability. Overall, the placebo control group exhibited no significant changes in liver injury markers (SGOT and SGPT), bilirubin, or systemic inflammation (CRP) during the study period. Although modest improvements were observed in serum albumin, total protein, and the A/G ratio, these changes were not accompanied by improvements in biochemical markers of hepatocellular injury or inflammation.

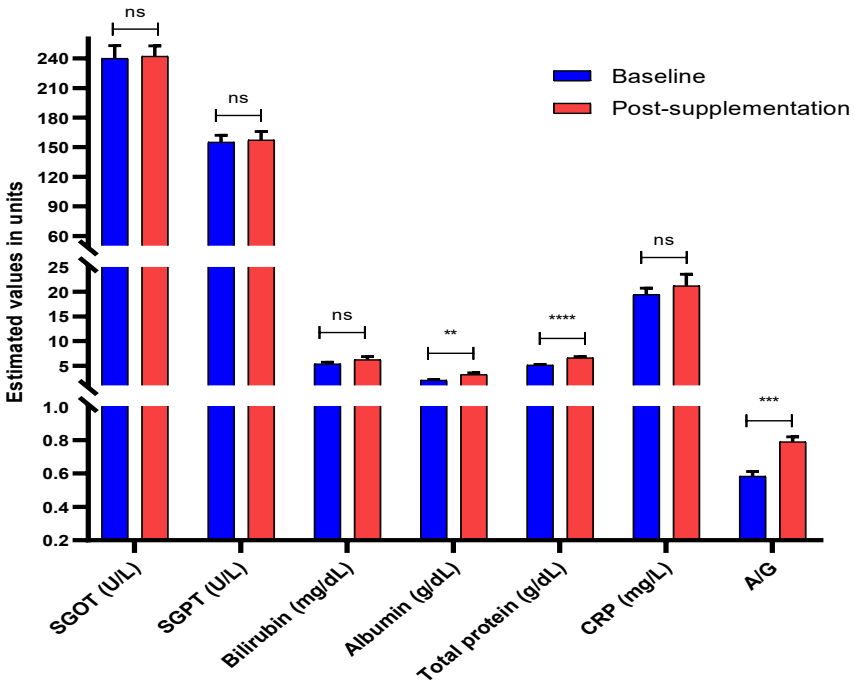


Figure 2: Effect of protein supplementation on biochemical parameters in patients with hepatic cirrhosis placebo control. Data are presented as mean ± SEM. Protein supplementation didn't show any effect on SGOT, SGPT, total bilirubin, and CRP levels while significantly increasing total albumin, total protein, and A/G ratio compared with baseline values. Statistical significance was determined using a paired t-test. ****p < 0.0001 versus baseline.

TABLE 2: Statistical analysis for liver function and inflammation parameter on protein supplementation on hepatic cirrhosis placebo group.

The effects of 8 weeks of protein supplementation on biochemical and nutritional parameters among healthy control subjects are presented in Figure 4. In contrast to the cirrhosis cohort, only modest changes were observed, reflecting the normal baseline physiological status of the participants.

	Significant	P value	Mean of Baseline	Mean of post-supplementation
SGOT (U/L)	No	0.900706	240.0	242.1
SGPT (U/L)	No	0.837505	155.0	157.3
Bilirubin (mg/dL)	No	0.210365	5.355	6.250
Albumin (g/dL)	Yes	0.001954	2.080	3.220
Total protein (g/dL)	Yes	<0.000001	5.125	6.640
CRP (mg/L)	No	0.499569	19.42	21.22
A/G	Yes	0.000012	0.5835	0.7900

Serum liver enzymes remained within the normal reference range throughout the study period. No statistically significant differences were observed in SGOT (AST) and SGPT (ALT) levels following supplementation. Mean SGOT values showed a slight decrease from approximately 28 U/L to 26 U/L, while SGPT decreased from approximately 25 U/L to 22 U/L; however, these changes were not significant (ns, $p > 0.05$). These findings indicate that protein supplementation did not adversely affect hepatic function in healthy individuals.

A modest but significant reduction in serum bilirubin concentration was observed after supplementation. Mean bilirubin levels decreased from approximately 0.80 mg/dL to 0.68 mg/dL ($p < 0.05$), suggesting improved metabolic efficiency while remaining within the physiological range. Markers of nutritional status demonstrated significant improvement following supplementation. Serum albumin levels increased significantly from approximately 4.4 g/dL to 4.7 g/dL ($p < 0.01$), while total protein concentrations increased from approximately 7.0 g/dL to 7.8 g/dL ($p < 0.001$). These findings indicate enhanced protein availability and improved nutritional reserves following regular protein intake.

A significant decrease in systemic inflammation was also observed. Mean CRP concentrations declined from approximately 1.6 mg/L to 1.2 mg/L ($p < 0.05$), indicating a reduction in low-grade inflammatory status. Although CRP levels were already within the normal range at baseline, supplementation appeared to confer additional anti-inflammatory benefits.

Furthermore, the albumin-to-globulin (A/G) ratio increased significantly from approximately 1.45 to 1.55 ($p < 0.001$), reflecting improved protein balance and nutritional status. Overall, protein supplementation in healthy controls did not significantly alter liver enzyme activities but produced favorable effects on protein status, inflammatory markers, and protein homeostasis. The magnitude of improvement was smaller than that observed in cirrhotic patients, which is expected given the absence of baseline nutritional deficiencies or hepatic dysfunction in the control group.

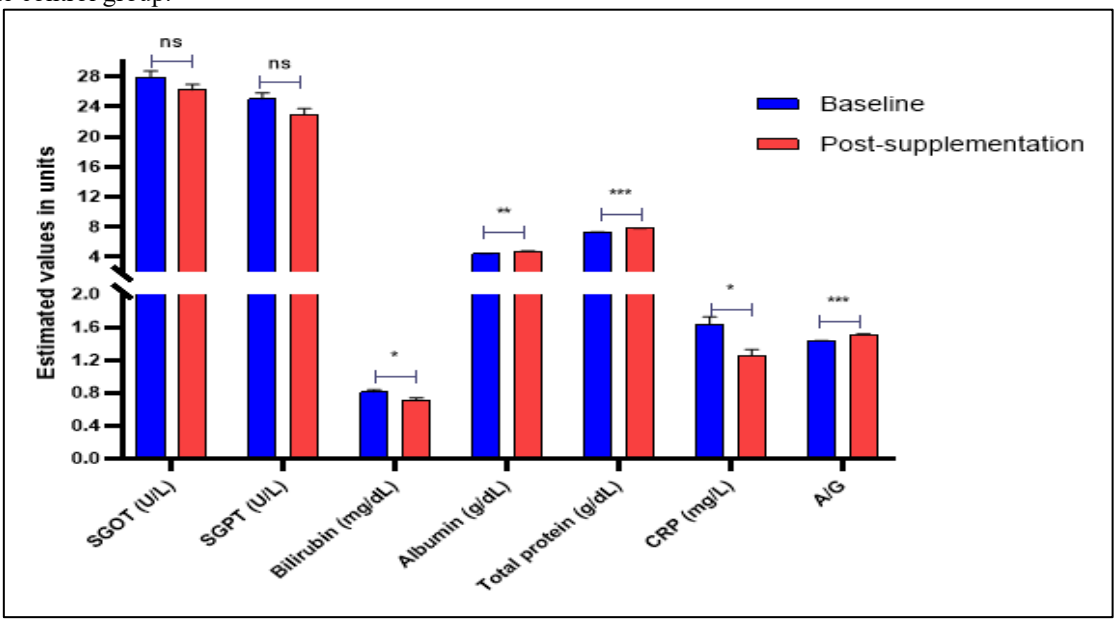


Figure 4: Effect of protein supplementation on biochemical and nutritional parameters in healthy control subjects. Data are presented as mean ± SEM. No significant changes were observed in SGOT and SGPT levels. Significant improvements were observed in serum bilirubin, albumin, total protein, CRP, and A/G ratio following supplementation. Statistical significance was determined using a paired t-test. *p < 0.05, **p < 0.01, ***p < 0.001; ns = not significant.

TABLE 4: Statistical analysis for liver function and inflammation parameter on protein supplementation control group

	Significant	P value	Mean of Baseline	Mean of post-supplementation
SGOT (U/L)	No	0.118502	27.95	26.20
SGPT (U/L)	No	0.070834	25.00	23.00
Bilirubin (mg/dL)	Yes	0.012754	0.8100	0.7100
Albumin (g/dL)	Yes	<0.000001	4.435	4.785
Total protein (g/dL)	Yes	<0.000001	7.305	7.805
CRP (mg/L)	Yes	0.001574	1.640	1.255
A/G	Yes	<0.000001	1.431	1.512

Effect of protein supplementation on lipid profile

The effect of protein supplementation on serum lipid parameters in patients with liver disorders is presented in Figure 5. Significant improvements were observed in total cholesterol and LDL cholesterol levels following the intervention, accompanied by a moderate reduction in triglyceride concentrations.

Serum lipid parameters demonstrated significant improvement following protein supplementation. Mean total cholesterol increased from approximately 143.6 mg/dL at baseline to 162 mg/dL post-intervention, representing an increase of approximately 14.1% ($p < 0.0001$). This increase is suggestive of improved hepatic synthetic activity and enhanced nutritional status, as reduced serum cholesterol concentrations are commonly observed in patients with advanced liver disease due to impaired cholesterol biosynthesis.

Similarly, low-density lipoprotein (LDL) cholesterol increased significantly from approximately 78 mg/dL to 90 mg/dL, corresponding to an increase of approximately 15.4% ($p < 0.0001$). Restoration of LDL cholesterol toward the normal physiological range reflects improved hepatic lipoprotein synthesis and recovery of lipid metabolic function. In patients with chronic liver disease, low LDL levels frequently result from impaired hepatic production rather than favorable cardiovascular status; therefore, moderate increases after nutritional intervention are considered indicative of metabolic and hepatic recovery.

In contrast, serum triglyceride concentrations showed a significant decline following supplementation. Mean triglyceride levels decreased from approximately 133 mg/dL at baseline to 126 mg/dL post-intervention, representing a reduction of approximately 6.8% ($p < 0.001$). This decrease suggests improved lipid utilization and regulation of triglyceride metabolism, potentially attributable to enhanced protein intake, improved energy metabolism, and restoration of hepatic metabolic function.

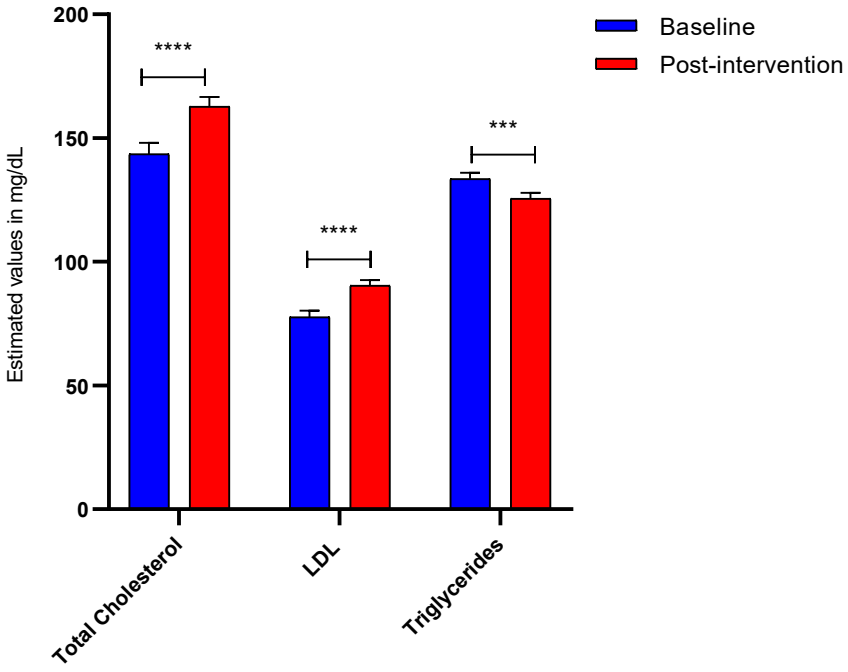


Figure 5: Effect of protein supplementation on lipid profile parameters in patients with liver disorders. Data are presented as mean ± SEM. Significant increases were observed in total cholesterol and LDL cholesterol levels following supplementation, while triglyceride concentrations decreased significantly. Statistical significance was determined using a paired t-test. ***p < 0.001, ****p < 0.0001 compared with baseline values.

TABLE 5: Statistical analysis for lipid profile on protein supplementation in

In the

	Significant	P value	Mean of Baseline	Mean of post-intervention
Total Cholesterol (mg/dL)	Yes	0.002269	143.6	162.8
LDL (mg/dL)	Yes	0.000636	77.70	90.40
Triglycerides (mg/dL)	Yes	0.020745	133.5	125.6

placebo control group, serum total cholesterol remained stable throughout the study period. Mean total cholesterol increased marginally from 114.1 mg/dL at baseline to 116.5 mg/dL post-intervention, representing an increase of approximately 2.1%; however, this difference was not statistically significant ($p = 0.6735$). These findings indicate that placebo administration did not significantly influence cholesterol metabolism or hepatic lipid synthesis.

Similarly, low-density lipoprotein (LDL) cholesterol showed only a minimal increase from 60.85 mg/dL to 62.21 mg/dL, corresponding to an increase of approximately 2.2%. This change was not statistically significant ($p = 0.6373$), suggesting that hepatic lipoprotein production remained unchanged during the intervention period. Likewise, serum triglyceride concentrations demonstrated a slight increase from 152.0 mg/dL at baseline to 154.0 mg/dL following the intervention, representing an increase of approximately 1.3%. The observed difference was not statistically significant ($p = 0.6201$), indicating no appreciable effect of placebo on triglyceride metabolism.

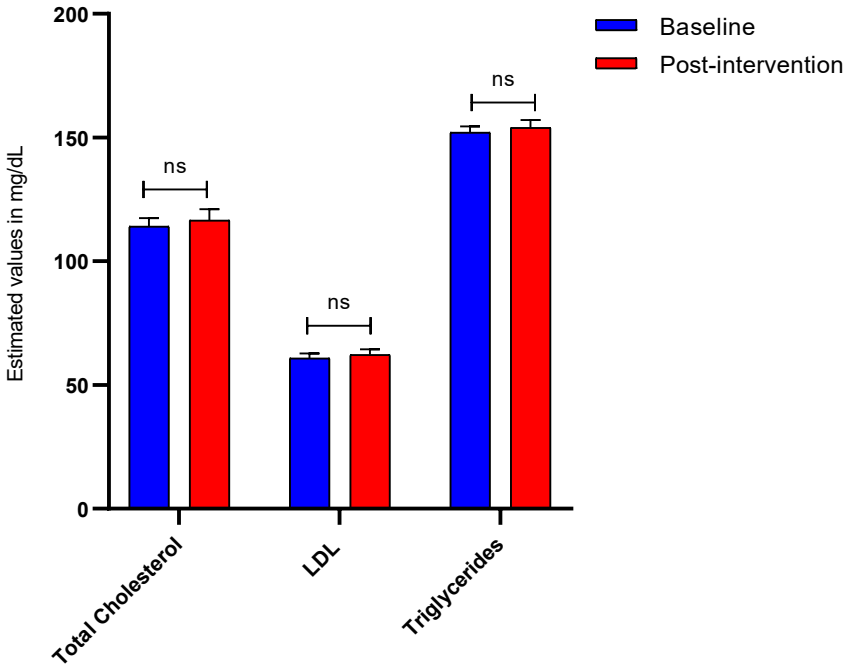


Figure 6: Effect of protein supplementation on lipid profile parameters in patients with hepatic cirrhosis placebo control. Data are presented as mean ± SEM. There were no significant difference was observed in total cholesterol, LDL and triglycerides levels following placebo treatment. Statistical significance was determined using a paired t-test. ns = not significant (p > 0.05).

TABLE 6: Statistical analysis for lipid profile on protein supplementation

The

	Significant	P value	Mean of Baseline	Mean of post-intervention
Total Cholesterol (mg/dL)	No	0.673469	114.1	116.5
LDL (mg/dL)	No	0.637251	60.85	62.21
Triglycerides (mg/dL)	No	0.620132	152.0	154.0

effects of protein supplementation on serum lipid parameters in healthy control subjects are presented in Figure 7. Unlike the liver disorder group, no statistically significant changes were observed in lipid profile parameters following the supplementation period, indicating maintenance of normal lipid homeostasis.

Mean total cholesterol increased marginally from approximately 180 mg/dL at baseline to 186 mg/dL post-supplementation; however, the difference was not statistically significant (ns, $p > 0.05$). Similarly, LDL cholesterol showed a slight increase from approximately 100 mg/dL to 104 mg/dL, which also failed to reach statistical significance (ns, $p > 0.05$). Triglyceride concentrations remained largely unchanged throughout the intervention

period. Mean triglyceride levels decreased slightly from approximately 125 mg/dL to 122 mg/dL, but the change was not statistically significant (ns, $p > 0.05$).

These findings indicate that protein supplementation did not adversely influence lipid metabolism in healthy individuals. The maintenance of lipid parameters within normal physiological ranges suggests that supplementation was metabolically well tolerated and did not induce clinically relevant alterations in cholesterol or triglyceride concentrations.

Overall, while significant improvements in lipid metabolism were observed among patients with liver disorders, healthy control subjects exhibited stable lipid profiles before and after supplementation. This differential response likely reflects the correction of pre-existing metabolic disturbances in cirrhotic patients, whereas healthy individuals already possessed normal lipid homeostasis at baseline.

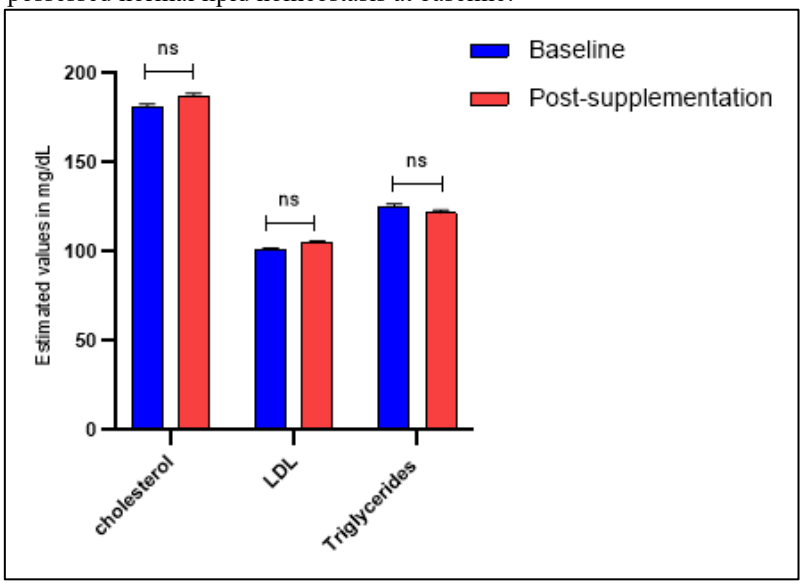


Figure 7: Effect of protein supplementation on lipid profile parameters in healthy control subjects. Data are presented as mean ± SEM. No significant differences were observed in total cholesterol, LDL cholesterol, or triglyceride concentrations following supplementation. Statistical significance was determined using a paired t-test. ns = not significant ($p > 0.05$).

TABLE 7: Statistical analysis for lipid profile on protein supplementation

Effect of intervention anthropometric parameters

The effects of protein supplementation on anthropometric parameters in patients with hepatic cirrhosis are presented in Figure 5. Significant improvements were observed in nutritional status following the intervention, as evidenced by increases in body mass index (BMI) and triceps skinfold (TSF) thickness. Mean BMI increased significantly from approximately 22.5 kg/m² at baseline to 24.0 kg/m² following intervention ($p < 0.001$). This improvement indicates enhanced nutritional status and a positive energy balance resulting from sustained protein supplementation. The increase in BMI is consistent with improved dietary intake and recovery from protein-energy malnutrition commonly observed in cirrhotic patients.

	Significant	P value	Mean of Baseline	Mean of post-supplementation
Total Cholesterol (mg/ml)	No	0.006595	181.3	187.3
LDL (mg/ml)	No	0.02599	100.9	104.9
Triglycerides (mg/ml)	No	0.110127	125.2	121.8

Body weight increased from approximately 67 kg to 71 kg after the intervention period. Although an upward trend was evident, the difference was not statistically significant (ns, $p > 0.05$). The lack of statistical significance may be attributable to inter-individual variability in body composition changes, fluid balance, and disease severity among participants.

A marked improvement was observed in TSF thickness, which increased significantly from approximately 12 mm at baseline to 15 mm post-intervention ($p < 0.0001$). TSF thickness is an established indicator of peripheral fat stores and nutritional reserves; therefore, the observed increase suggests restoration of body fat mass and improved nutritional rehabilitation following supplementation.

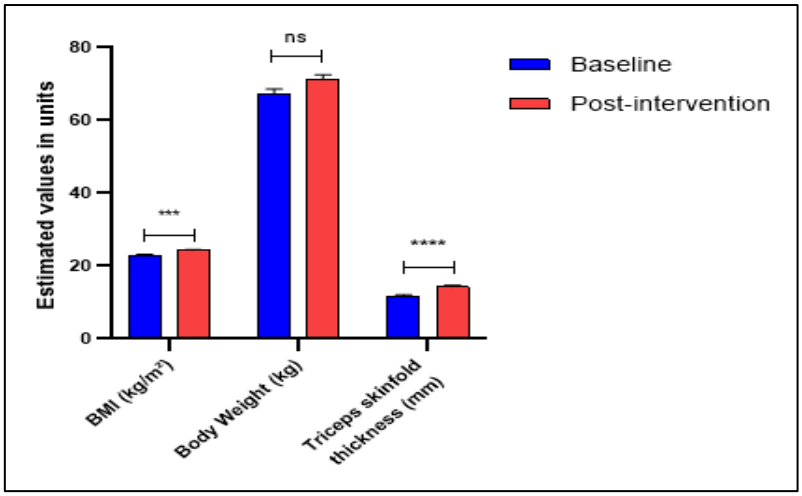


Figure 8: Effect of protein supplementation on anthropometric parameters in patients with hepatic cirrhosis. Data are presented as mean ± SEM. Significant increases were observed in BMI and triceps skinfold (TSF) thickness following supplementation, whereas body weight showed a non-significant increasing trend. Statistical significance was determined using a paired t-test. ***p < 0.001, ****p < 0.0001; ns = not significant.

TABLE 8: Statistical analysis for anthropometric parameters on protein supplementation among patients

	Significant	P value	Mean of Baseline	Mean of post-intervention
BMI (kg/m²)	Yes	0.000219	23.01	24.27
Body Weight (kg)	No	0.050144	67.3	71.18
Triceps skinfold thickness (mm)	Yes	0.000162	11.58	14.33

Anthropometric parameters remained largely unchanged in the placebo control group throughout the study period. Mean body mass index (BMI) increased modestly from 23.21 kg/m² at baseline to 24.40 kg/m² post-intervention, representing an increase of approximately 5.1%. However, this difference was not statistically significant (p = 0.1030), indicating that the placebo intervention did not produce a meaningful improvement in overall nutritional status.

Similarly, body weight increased slightly from 69.70 kg at baseline to 71.33 kg following the intervention, corresponding to an increase of approximately 2.3%. This change was not statistically significant (p = 0.6739), suggesting that the observed increase was within the range of normal biological variation rather than a true intervention effect.

Likewise, triceps skinfold thickness, an indicator of peripheral fat stores, increased from 9.50 mm to 10.65 mm, representing an increase of approximately 12.1%. Despite this numerical increase, the difference was not statistically significant (p = 0.1713), indicating that subcutaneous fat reserves remained essentially unchanged during the study period.

Overall, the placebo control group exhibited no significant improvements in anthropometric indices, including BMI, body weight, and triceps skinfold thickness. These findings suggest that placebo administration did not substantially influence body composition or nutritional status.

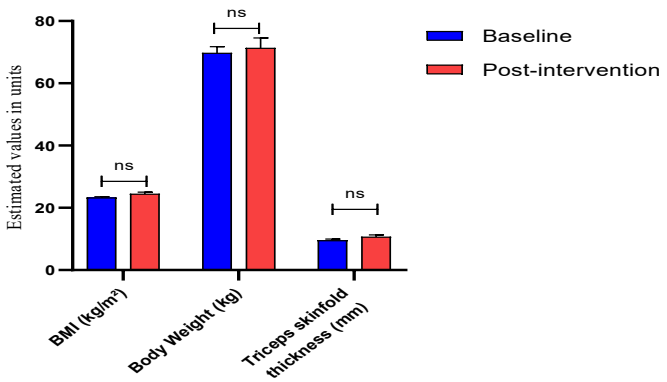


Figure 9: Effect of protein supplementation on anthropometric parameters in patients with hepatic cirrhosis placebo control. Data are presented as mean ± SEM. No significant difference was observed in BMI, body weight and triceps skinfold (TSF) thickness following placebo supplementation, Statistical significance was determined using a paired t-test. ns = not significant (p > 0.05)

TABLE 9: Statistical analysis for anthropometric parameters on protein supplementation among patients

	Significance	P value	Mean of Baseline	Mean of post-intervention
BMI (kg/m²)	No	0.102962	23.21	24.40
Body Weight (kg)	No	0.673864	69.70	71.33
Triceps skinfold thickness (mm)	No	0.171343	9.500	10.65

The effects of protein supplementation on anthropometric parameters in healthy control subjects are presented in Figure 6. Following the supplementation period, slight increases were observed in body mass index (BMI), body weight, and triceps skinfold (TSF) thickness; however, none of these changes reached statistical significance, indicating maintenance of normal nutritional status throughout the study.

Mean BMI increased marginally from approximately 23.5 kg/m² at baseline to 24.5 kg/m² post-supplementation, but the difference was not statistically significant (ns, $p > 0.05$). Similarly, body weight increased from approximately 68 kg to 72 kg, showing a positive trend without statistical significance (ns, $p > 0.05$).

TSF thickness also demonstrated a modest increase from approximately 16 mm at baseline to 18 mm following supplementation. Despite the numerical improvement, the difference remained statistically non-significant (ns, $p > 0.05$).

The absence of significant changes is expected because the control participants were apparently healthy individuals with normal baseline anthropometric values and adequate nutritional status. Consequently, the supplementation primarily maintained normal body composition rather than producing substantial gains.

Overall, protein supplementation was well tolerated and supported the maintenance of healthy anthropometric parameters without causing excessive weight gain or alterations in body composition. In contrast to cirrhotic patients, where significant nutritional recovery was observed, healthy controls exhibited stable anthropometric measurements throughout the intervention period.

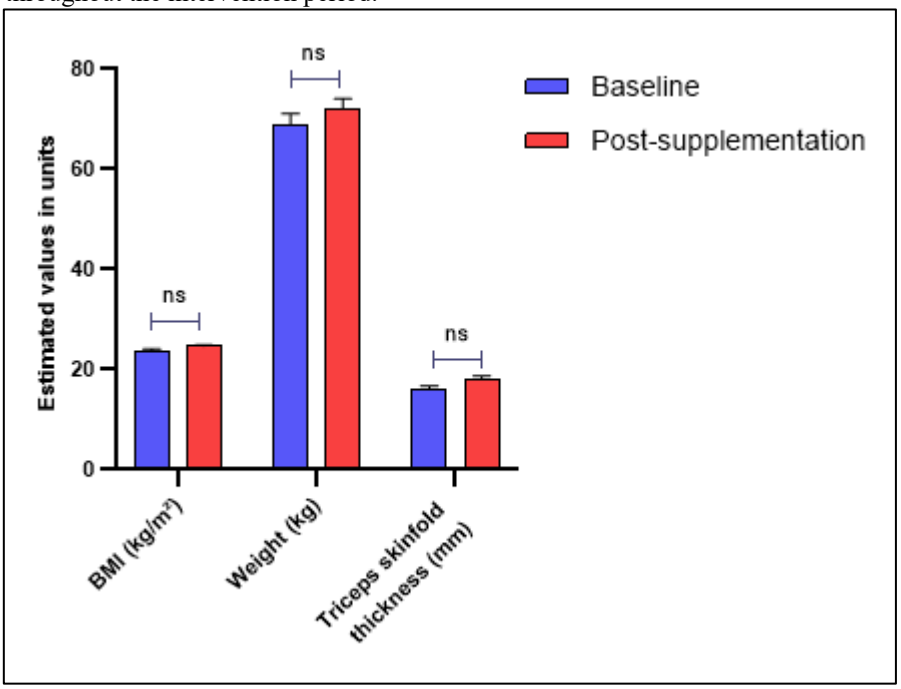


Figure 10: Effect of protein supplementation on anthropometric parameters in healthy control subjects. Data are presented as mean ± SEM. No significant differences were observed in BMI, body weight, or triceps skinfold (TSF) thickness following supplementation. Statistical significance was determined using a paired t-test. ns = not significant ($p > 0.05$).

TABLE 10: Statistical analysis for anthropometric parameters on protein supplementation among control subjects

	Significant	P value	Mean of Baseline	Mean of post-supplementation
BMI (kg/m²)	No	0.022465	23.84	24.67
Weight (kg)	No	0.319393	69.05	72.00
Triceps skinfold thickness (mm)	No	0.006388	16.20	18.20

Effect of protein intervention on Quality of Life & Functional Outcomes

The effects of protein supplementation on fatigue severity, appetite, and disease-specific quality of life among patients with hepatic cirrhosis are presented in Figure 7. Significant improvements were observed in all patient-

reported outcome measures following the intervention period, indicating enhanced physical well-being, nutritional intake, and overall quality of life.

Fatigue severity, assessed using the Fatigue Severity Scale (FSS), decreased significantly following protein supplementation. The mean FSS score declined from approximately 6.2 at baseline to 4.1 post-intervention ($p < 0.0001$), representing a reduction of nearly 34%. This finding suggests a substantial alleviation of fatigue symptoms, one of the most common and debilitating complaints among patients with chronic liver disease.

Appetite status, evaluated using the Simplified Nutritional Appetite Questionnaire (SNAQ), improved markedly after supplementation. Mean SNAQ scores increased from approximately 9.5 at baseline to 13.8 following intervention ($p < 0.0001$). The significant improvement in appetite indicates enhanced dietary intake and better nutritional behavior, which likely contributed to the observed improvements in anthropometric and biochemical parameters. Similarly, disease-specific quality of life, assessed using the Chronic Liver Disease Questionnaire (CLDQ), demonstrated significant enhancement. Mean CLDQ scores increased from approximately 3.8 to 5.3 ($p < 0.0001$) following supplementation, reflecting improvements in physical functioning, emotional well-being, activity levels, and overall health perception.

Collectively, these findings demonstrate that protein supplementation not only improved biochemical and nutritional markers but also produced clinically meaningful benefits in patient-centered outcomes. The reduction in fatigue and the concurrent improvements in appetite and quality of life suggest a positive impact of nutritional intervention on the overall health status and daily functioning of patients with hepatic cirrhosis.

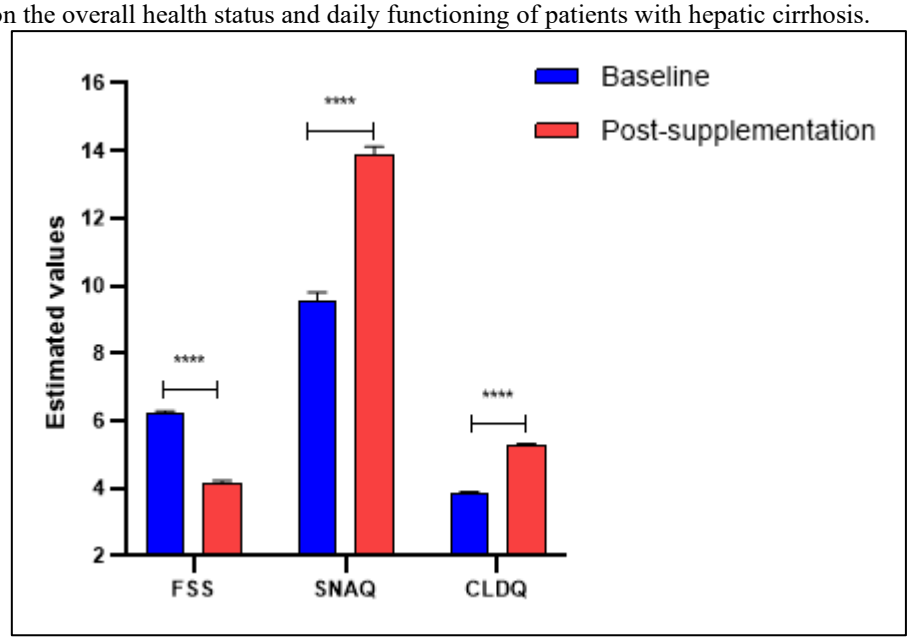


Figure 11: Effect of protein supplementation on fatigue severity, appetite, and disease-specific quality of life in patients with hepatic cirrhosis. Data are presented as mean ± SD. Significant reductions in Fatigue Severity Scale (FSS) scores and significant increases in Simplified Nutritional Appetite Questionnaire (SNAQ) and Chronic Liver Disease Questionnaire (CLDQ) scores were observed following supplementation. Statistical significance was determined using a paired t-test. ****p < 0.0001 compared with baseline values.

TABLE 11: Statistical analysis for Quality of Life & Functional Outcomes on protein supplementation among patients

	Significant	P value	Mean of Baseline	Mean of post-supplementation
FSS	Yes	<0.000001	6.218	4.163
CLDQ	Yes	<0.000001	3.853	5.275
SNAQ	Yes	<0.000001	9.550	13.88

DISCUSSION

The present prospective cohort study evaluated the impact of 8 weeks of protein supplementation on biochemical, nutritional, anthropometric, inflammatory, and quality-of-life parameters in patients with hepatic cirrhosis. The findings demonstrated significant improvements in liver function biomarkers, nutritional status, lipid metabolism, systemic inflammation, fatigue, appetite, and disease-specific quality of life following supplementation. These results emphasize the critical role of nutritional intervention as an adjunct therapeutic strategy in the management of chronic liver disease.

Protein-energy malnutrition is a hallmark of advanced cirrhosis and is associated with reduced hepatic protein synthesis, sarcopenia, impaired immunity, and poor survival (17,11). The present study supplements are enriched in BCAAs and are primarily metabolized in skeletal muscle rather than the liver, allowing them to serve as an

efficient nutritional substrate even in patients with impaired hepatic function. Cirrhosis is also characterized by depletion of circulating BCAAs and a reduced Fischer ratio, which contributes to impaired protein synthesis, altered nitrogen metabolism, and hepatic encephalopathy. Supplementation with leucine, isoleucine, and valine replenishes these deficiencies, thereby improving whole-body protein metabolism and nutritional status (18,12).

In the present study, protein supplementation(Hepapro) for 8 weeks significantly improved liver function biomarkers, nutritional status, anthropometric indices, inflammatory markers, and patient-reported outcomes in cirrhotic patients.

A significant reduction in serum SGOT and SGPT levels was observed following supplementation, indicating attenuation of hepatocellular injury. These findings are consistent with previous studies demonstrating that adequate protein intake and amino acid supplementation improve metabolic homeostasis and hepatic function in cirrhotic patients (19,20). Improved nutritional status may enhance hepatic regeneration and reduce oxidative stress, thereby contributing to the observed reduction in liver enzyme activities.

Although BCAAs are not directly hepatoprotective, experimental evidence suggests that they improve mitochondrial bioenergetics, reduce oxidative stress, and suppress inflammatory signaling pathways involved in chronic liver injury. Leucine has been shown to modulate cellular energy metabolism, while isoleucine and valine contribute to improved mitochondrial function and reduction of reactive oxygen species (12,20-23). Furthermore, BCAAs suppress activation of nuclear factor-κB (NF-κB), resulting in decreased production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, thereby limiting chronic hepatocyte injury (24). These mechanisms likely contributed to the significant decline in liver enzyme activities observed in the intervention group.

The marked reduction in serum bilirubin concentrations following supplementation suggests improvement in hepatic excretory function. Merli et al. reported that nutritional optimization in cirrhotic patients positively influences clinical outcomes and liver function parameters, including bilirubin levels (12). Furthermore, nutritional support has been shown to improve hepatic reserve and delay disease progression in chronic liver disease patients (25).

One of the most notable findings of the present study was the significant increase in serum albumin, total protein, and A/G ratio. Hypoalbuminemia is a recognized predictor of poor prognosis in cirrhosis and reflects both impaired hepatic synthetic capacity and malnutrition (26). Previous investigations have shown that adequate dietary protein intake improves nitrogen balance and promotes protein synthesis in cirrhotic individuals without worsening hepatic encephalopathy (27,28). The observed improvements in albumin and total protein levels therefore indicate enhanced nutritional rehabilitation and restoration of hepatic synthetic function. Among the BCAAs, leucine plays a central regulatory role by activating the phosphatidylinositol-3 kinase (PI3K)/Akt/mammalian target of rapamycin complex-1 (mTORC1) signaling pathway, which stimulates translation initiation and hepatic protein synthesis. Activation of mTORC1 promotes phosphorylation of downstream effectors such as S6 kinase and 4E-binding protein-1, thereby enhancing albumin synthesis and improving nitrogen retention (29,30). The observed increase in serum albumin therefore reflects not only improved nutritional intake but also enhanced hepatic synthetic function mediated by leucine-induced anabolic signaling. Improved total protein concentrations and restoration of the A/G ratio further support recovery of protein homeostasis.

Systemic inflammation plays a critical role in cirrhosis progression and complications. In the present study, CRP levels decreased significantly after supplementation. Similar findings have been reported in nutritional intervention studies where improved protein intake reduced inflammatory burden and enhanced immune competence (31). Reduced inflammation may further contribute to improved hepatic function and overall clinical status.

Interestingly, significant increases in total cholesterol and LDL cholesterol were observed after supplementation, whereas triglyceride levels declined. Reduced serum cholesterol concentrations are commonly observed in advanced liver disease due to impaired hepatic synthesis of lipoproteins (32). Therefore, normalization of cholesterol and LDL levels in the present study is likely reflected in improved hepatic synthetic activity rather than adverse metabolic consequences. Similar observations have been documented during nutritional rehabilitation of cirrhotic patients (33).

Anthropometric assessment demonstrated significant improvements in BMI and triceps skinfold thickness. Malnutrition, sarcopenia, and loss of adipose tissue are highly prevalent in cirrhosis and are strongly associated with adverse outcomes (34). Restoration of BMI and TSF thickness following supplementation indicates replenishment of energy reserves and improvement in overall nutritional status (35). Similar benefits of nutritional support on body composition have been reported by Hanai et al. and Montano-Loza, who highlighted the prognostic significance of maintaining muscle and fat mass in chronic liver disease (8,9). BCAAs facilitate ammonia detoxification by promoting glutamine synthesis within skeletal muscle, thereby preserving muscle mass and improving nitrogen balance (36). Consequently, significant improvements in BMI and triceps skinfold thickness observed in the present study likely reflect enhanced protein accretion and improved body composition (37).

The present study also demonstrated significant reductions in fatigue severity together with improvements in appetite and disease-specific quality of life. Fatigue is one of the most debilitating symptoms of chronic liver disease and is often associated with poor nutritional status and impaired physical function (38). Improved nutritional intake following supplementation may enhance energy metabolism and physical performance, thereby reducing fatigue. Furthermore, significant improvements in CLDQ scores indicate better physical, emotional, and

social functioning. Similar improvements in health-related quality of life following nutritional interventions have been reported in patients receiving oral nutritional supplements and branched-chain amino acid formulations (39,40). In contrast, healthy control subjects showed only modest changes in biochemical and anthropometric parameters, which is expected because baseline values were already within normal physiological ranges. The absence of adverse effects further supports the safety and tolerability of the protein supplement. BCAAs serve as alternative energy substrates for skeletal muscle by generating acetyl-CoA and succinyl-CoA, thereby supporting ATP production through the tricarboxylic acid cycle (41). Improved muscle metabolism, reduced inflammation, and enhanced nutritional status may collectively explain the marked reduction in fatigue together with improvements in appetite and Chronic Liver Disease Questionnaire scores observed after supplementation.

An important strength of the present study is the inclusion of a placebo control group. Unlike the intervention group, placebo-treated patients demonstrated no significant improvements in liver enzymes, bilirubin, inflammatory markers, lipid profile, or anthropometric indices, suggesting that routine medical care alone was insufficient to produce meaningful metabolic recovery during the study period. The marked differences between the intervention and placebo groups therefore strengthen the conclusion that the observed biochemical and clinical improvements are attributable to the metabolic actions of BCAA-enriched protein supplementation rather than spontaneous recovery or placebo effects.

CONCLUSION

The present findings suggest that supplementation with a SAMe, BCAA-enriched protein formulation improves multiple aspects of cirrhosis by simultaneously stimulating hepatic protein synthesis, restoring amino acid balance, enhancing ammonia detoxification, suppressing systemic inflammation, improving lipid metabolism, preserving skeletal muscle mass, and promoting hepatocyte recovery. These complementary mechanisms provide a strong biological rationale for incorporating SAMe and BCAA-containing protein supplements as an adjunctive Medical nutritional therapy in the comprehensive management of patients with liver diseases(Acute to Chronic conditions).

STRENGTHS AND LIMITATIONS

A major strength of this study is its randomized, placebo-controlled design involving participants recruited from multiple tertiary care centers. The study incorporated a comprehensive assessment of clinical, biochemical, anthropometric, inflammatory, and patient-reported outcomes, providing a holistic evaluation of the impact of protein supplementation in patients with chronic liver disease. The inclusion of both placebo and healthy control groups further strengthened the comparative analysis.

However, the study also has certain limitations. Although conducted across multiple centers, the sample size was relatively modest, which may limit the generalizability of the findings. The intervention period was of limited duration and did not permit assessment of long-term clinical outcomes. In addition, dietary intake and physical activity outside the prescribed intervention were not continuously monitored. Future large-scale, multicenter studies with longer follow-up periods are warranted to validate these findings and evaluate the long-term effects of protein supplementation on disease progression, hospitalization, and survival.

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