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Comparative Clinical Efficacy Between High And Low Branched Chain Amino Acid Enriched Whey Protein Formulas In Cachectic Hypoalbumenic Hospitalized Patients

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Abstract

Objectives: Cachexia is a dysregulation of fat, protein, and carbohydrate metabolism largely due to cytokine excess; ultimately resulting in severe wasting of the body's lean body mass (LBM), albumin, and branched-chain amino acids (BCAA) depletion. Whey protein (WP) is of superior quality due to its high digestibility and absorbability. In addition, WP is an excellent source of BCAAs: comprising 12% leucine and 26% total BCCA by weight, yielding a Leucine: Isoleucine: Valine ratio of approximately 4:1:1, respectively. Leucine is uniquely characterized by its anabolic effect rather than the anticatabolic effect and has been proven beneficial in mitigating protein wasting in critically ill patients. The aim of this study is to evaluate the clinical differences between two commercially available WP formulas that differ in BCAAs enrichment proportion.

Methods: A retrospective analysis was conducted in our institution between April 2017 and June 2019. Patient who had 2≤ episodes of diarrhea or failed to complete one week of hospital admission were excluded. All patients' continuous variables were analyzed using Independent Samples and One-Sample T-test while categorical data were expressed as numbers with percentages by using Chi Square test.

Results: Group I (%BCAAs≥20%) demonstrated a significantly shorter length of stay (LOS) and lower overall 28-day mortality compared with Group II (%BCAAs≈12%) with Mean±SD of (9.80±1.79 days vs. 12.00±2.33 days) and Mean percentage of (20.97% vs. 13.33%), respectively. Percent changes in albumin level (%ΔALB) were significantly higher in Group I compared with Group II (35.3%±4.64% vs. 28.3%±5.49%).

Conclusion: BCAAs enriched WP formula was superior to standard WP formula in stimulating ALB synthesis and LBM anabolism/catabolism ratio in cachexic hospitalized hypoalbuminemic patients.

Keywords: Branched-chain amino acids, Cachectic hospitalized patients, Hypoalbumenia, Leucine anabolic/anticatabolic ratio, Major clinical outcomes, Modular protein formulas, Whey protein.

Introduction

Most critically ill patients are incapacitated by wasting syndromes. Protein catabolism is inexorably hastened by the systemic inflammation associated with illness and demonstrated by elevated serum C-reactive protein (CRP)

levels.[1–3] The hypercatabolic state has been proven detrimental not only to LBM, but to visceral proteins as well.[4] Consequently, hypoalbuminemia is a pronounced finding in hospitalized patients and independently predicts an increased risk of post-surgical infections, increased hospital LOS and mortality.[5,6] However, ALB, among other proteins, is a negative acute phase reactant and is profoundly influenced by vascular permeability and thus cannot be used to attest to the nutritional status of the acutely ill unless it is matched to CRP in a more predictive CRP:ALB ratio.[7] In the critical care setting, muscle wasting secondary to immobility, inflammation, anorexia and drugs such as corticosteroids and neuromuscular blockers, termed critical illness myopathy (CIM) or intensive care unit-acquired weakness (ICUAW), delays weaning from mechanical ventilation and is associated with poor clinical outcomes.[8–11]

To mitigate the certain erosion of protein and its subsequent complications: measures must be taken to either reduce catabolism, stimulate anabolism, or both. The role of WP in stimulating protein anabolism has been well established.[12,13] WP is particularly superior to other proteins such as casein due to its unique characteristics. WP is a profound source of BCAAs, most importantly the anabolic amino-acid leucine.[11,12,14–16] Additionally, WP has a shorter gastrointestinal transit time than casein, and is hydrolyzed at a faster rate; enabling its absorption and more readily spiking postprandial serum amino acid concentration.[17]

The aim of this study is to evaluate the clinical differences between two commercially available WP formulas: BCAAs enriched (±20% Leucine) WP formula (**Formula I**) and standard (±12% Leucine) WP formula (**Formula II**). The primary gauged outcomes in the present study are %ΔALB and percentage changes CRP to albumin ratio (%ΔCRP: ALB). Other secondary outcomes that we intended to investigate include overall hospital length of stay (LOS), and overall 28-day hospital mortality.

Methods and Materials

A retrospective analysis was conducted at our King Hussein Medical Hospital (KHMH) for patients who were admitted between April 2017 and June 2019 and for whom we could obtain baseline demographics, diagnostics, anthropometrics, nutritional indices, and enteral modular protein formulas (MPFs) from our institutional electronic health record (Hakeem) or admitted patient's Kardex. Exclusion criteria in this study were: death or discharge before at least one week of admission or having 2 consecutive episodes of diarrhea.

All patient's continuous variables were analyzed by using the Independent Samples T-test to express the Means±SDs and Mean differences±SEMs for cachectic hypoalbumenic hospitalized patients who were on Formula I (Group I) and cachectic hypoalbumenic hospitalized patients who were on Formula II (Group II). All, Group I, and Group II categorical data were expressed as numbers with percentages by using the Chi Square Test. Statistical analyses were performed using IBM SPSS version. 25 (IBM Corp., Armonk, NY, USA) and P-values ±0.05 were considered statistically significant. Patients selection and data collection process are outlined in **Fig.1**

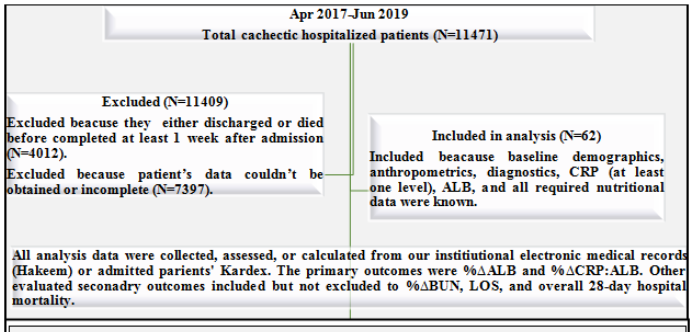

Fig 1. Flow chart of cachexic hypoalbuminemic patient's selection and data collection process.

Apr: April. CRP: C-reactive protein.
CRP:ALB: CRP to ALB ratio.
Jun: June. LOS: Length of stay
ALB: Albumin.
N: Number of studied patients. BUN: Blood urea nitrogen.
%Δ: Percent changes.

Results

There was no significant difference in age between the two studied groups. Group I demonstrated a significantly shorter LOS and lower overall 28-day mortality compared with Group II, with Mean±SD of (9.80±1.79 days vs. 12.00±2.33 days) and Mean percentage of (20.97% vs. 13.33%), respectively. There was no significant difference regarding gastrointestinal symptoms, including diarrhea, between the two groups. Furthermore, no significant differences in baseline Gastric residual volumes (GRV) nor in GRVs measured one week after admission were observed, however, the percent changes in GRV were significantly lower in Group I with Mean±SD 17.0%±6.98% in Group I vs. 20.4%±3.77% in Group II.

The nutritional indices of total calorie input (TCI) and protein density (PD) were (1042.0±183.9 Cal/day vs. 1148.7±202.4 Cal/day) and (4.39±0.49 g/100Cal/day vs. 4.37±0.64 g/100Cal/day) in Group I vs. Group II, respectively. The primary outcomes; %ΔCRP and %ΔALB were significantly higher in Group I (133.8%±24.26% vs. 113.2%±18.55%) (35.3%±4.64% vs. 28.3%±5.49%) for Group I vs. Group II. However, the difference in the Mean±SD of %ΔCRP:ALB ratio was not significant (73.4%±22.31%vs. 66.5%±16.78%) for Group I vs. Group II.

CRP was significantly higher in Group I both at baseline and after one week (11.57±1.67 mg/dl and 26.78±2.77mg/dl) vs. (9.30±1.75 mg/dl and 19.77±3.60 mg/dl) for Group II. Regarding ALB, Group II had significantly higher ALBs than Group I both at baseline (2.43±0.09 g/dl vs. 2.58±0.14 g/dl) and after one week (3.28±0.01 g/dl vs. 3.30±0.04 g/dl) for Means±SDs of Group I vs. Group II, respectively. The ALB must be seen considering the significantly higher Mean±SD of human albumin (H.ALB) administered intravenously in Group II at 20.00±0.00 g/day for Group II vs. 9.00±3.05 g/day in Group I.

Additionally, the baseline BUN was significantly higher in Group I vs. Group II with 14.06±3.48 mg/dl vs. 11.12±2.59 mg/dl. After at least one week, the BUN in Group I remained significantly higher than Group II with Mean±SD of 14.57±0.32 mg/dl vs. 12.31±2.37 mg/dl. Finally, the Means differences±SEMs for Group I vs. Group II of %Δ ALB, %Δ CRP, %Δ CRP:ALB ratio, and Overall Hospital LOS were 6.95%±1.29%, 20.64%±5.51%, 6.93%±5.04%, and -2.20±0.53 days, respectively. Demographics, admission diagnostics and wards, anthropometrics, nutritional indices and follow-up comparison data of the study's cachectic hospitalized patients are summarized in **Tables 1-2.**

Table 1. Demographics, admission diagnostics and wards, tolerance rates, and mortalities of the study's cachectic hospitalized patients.

Variables		Total N (%) (N=62)	Group I N (%) (N=30)	Group II N (%) (N=32)	P-Value
Gender	Female	21 (33.87%)	9 (30.0%)	12 (37.5%)	0.826 (NS)
	Male	41 (66.13%)	21 (70.0%)	20 (62.5%)	
Ward	Non-Critical unit	29 (46.77%)	14 (46.66%)	15 (46.89%)	0.312 (NS)
	Critical unit	33 (53.23%)	16 (53.33%)	17 (53.13%)	
Medical Dx	Medical	27 (43.55%)	13 (43.33%)	14 (43.75%)	0.556 (NS)

	Surgical	35 (56.45%)	17 (56.66%)	18 (56.25%)	
Tolerance	GI Sx (0,1)	38 (61.29%)	19 (63.33%)	19 (59.38%)	0.303 (NS)
	GI Sx (≥2)	24 (38.71%)	11 (36.66%)	13 (40.63%)	
Diarrhea	No (<3 loose stool/day)	40 (64.52%)	20 (66.66%)	20 (62.50%)	0.221 (NS)
	Yes (≥3 loose stool/day)	22 (35.48%)	10 (33.33%)	12 (37.5%)	
Mortality	Overall 28-day Survival	49 (79.03%)	26 (86.66%)	23 (71.88%)	0.001 (S)
	Overall 28-day Mortality	13 (20.97%)	4 (13.33%)	9 (28.13%)	

Data were presented as number (percentage) by using the Chi Square test.

Group I: Cachectic hospitalized patients who received BCAAs enriched WP formula (Formula I).

Group II: Cachectic hospitalized patients who received standard WP formula (Formula II).

S: Significant (P-Value <0.05).

NS: Non-significant (P-Value >0.05).

N: Number of study's hospitalized patients.

GI: Gastrointestinal.

Sx: Symptoms.

Dx: Diagnosis.

Discussion

The present retrospective study of 62 cachexic hypoalbuminemic patients investigated the effect of WP with two different percentages of BCAAs on protein metabolism. During critical illness, major changes in protein metabolism occur: A shift in the prioritization of protein synthesis takes place in the liver, favoring the synthesis of positive acute phase reactants at the expense of negative phase reactants such as ALB.[18] Cachexia accompanies an array of diseases, the exact mechanism remains unclear, however, cytokines appear to play a pivotal role in the pathophysiology of cachexia. Cytokines negatively affect protein synthesis at a nuclear level. Leading to loss of the major loss of muscle mass associated with increased mortality.[19,20] To ameliorate the catabolism occurring to adapt to the increased demand associated with a critical illness, Protein must be provided exogenously to spare the structural and visceral proteins from catabolism. [7,21] To further support the provision of protein in critically ill patients, an observational cohort study of 113 ICU patients, Allingstrup *et al* concluded that higher protein administration reduced overall 28-day mortality[22]

Table 2. Anthropometrics and nutritional indices and follow-up comparison data of the study's cachectic hospitalized patients.

Variables	Group I(Mean±SD) (N=30)	Group II (Mean±SD) (N=32)	Group I vs Group II Mean differences ± SEM	P-Value
Age (Yrs)	61.13±10.55	58.91±8.89	2.23±2.47	0.371 (NS)
BW (Kg)	82.09±8.79	75.98±11.60	6.11±2.63	0.023 (S)
BMI (Kg/m^2)	29.31±2.48	26.76±4.64	2.55±0.95	0.010 (S)
CRP_1 (mg/dl)	11.57±1.67	9.30±1.75	2.27±0.43	0.000 (S)
ALB_1 (g/dl)	2.43±0.09	2.58±0.14	-0.15±0.03	0.002 (S)
CRP: ALB $Ratio_1$ (X: 1)	4.79±0.89	3.65±0.87	1.14±0.22	0.000 (S)

BUN_1 (mg/dl)	14.06±3.48	11.12±2.59	2.95±0.78	0.000 (S)
CRP_2 (mg/dl)	26.78±2.77	19.77±3.60	7.00±0.81	0.000 (S)
ALB_2 (g/dl)	3.28±0.01	3.30±0.04	-0.02±0.01	0.000 (S)
CRP: ALB $Ratio_2$ (X: 1)	8.16±0.86	5.99±1.13	2.16±0.25	0.000 (S)
BUN_2 (mg/dl)	14.57±0.32	12.31±2.37	2.26±0.42	0.000 (S)
H.ALB (g/day)	9.00±3.05	20.00±0.00	-11.00±5.41	0.000 (S)
%Δ ALB	35.3%±4.64%	28.3%±5.49%	6.95%±1.29%	0.000 (S)
%Δ CRP	133.8%±24.26%	113.2%±18.55%	20.64%±5.51%	0.000 (S)
%Δ CRP:ALB ratio	73.4%±22.31%	66.5%±16.78%	6.93%±5.04%	0.174 (NS)
%ΔBUN	8.81%±22.85%	13.3%±27.19%	-4.44%±6.36%	0.488 (NS)
TCI (Cal/Kg/day)	14.83±2.29	16.75±2.38	-1.92±0.59	0.002 (S)
TCI (Cal/day)	1042.0±183.9	1148.7±202.4	-106.7±49.23	0.034 (S)
PD (g/100Cal/day)	4.39±0.49	4.37±0.64	0.03±0.15	0.864 (NS)
Mg (mg/dl)	2.31±0.02	2.31±0.01	0.00±0.00	0.885 (NS)
K (mEq/l)	4.19±0.09	4.06±0.09	0.13±0.02	0.000 (S)
PO_4 (mg/dl)	3.32±0.34	3.33±0.25	-0.01±0.07	0.923 (NS)
GRV_1 (ml)	144.7±6.69	144.5±5.52	0.19±1.56	0.906 (NS)
GRV_2 (ml)	169.9±15.62	174.0±9.32	-4.35±3.29	0.192 (NS)
%ΔGRV	17.0%±6.98%	20.4%±3.77%	-3.31%±1.44%	0.025 (S)
Overall Hospital LOS	9.80±1.79	12.00±2.33	-2.20±0.53	0.000 (S)

Data were presented as Mean±SD and Mean difference±SEM by using the Independent T-test.

Group I: Cachectic hospitalized patients who received BCAAs enriched WP formula (Formula I).

Group II: Cachectic hospitalized patients who received standard WP formula (Formula II).

Yrs: Years.

BW: Actual body weight.

BMI: Body mass index.

1: baseline at admission.

2: 1 week after admission.

%Δ: Percentage of Changes.

S: Significant (P-Value <0.05).

NS: Non-significant (P-Value >0.05).

N: Number of study's hospitalized patients.

ALB: Albumin level.

Cal: Calories.

H.ALB: Human albumin.

PD: Protein density.

CRP: C-reactive protein.

CRP: ALB: CRP to ALB ratio.

Mg: Total corrected serum magnesium level.

K: Serum corrected potassium level.

PO_4: Serum phosphate level.

BUN: Blood urea nitrogen.

TCI: Total calorie input.

GRV: Gastric residual volume.

LOS: Length of stay $day_{(s)}$.

WP administration has been proven efficacious in stimulating protein anabolism.[13] WP's anabolic effects may be attributed to its high BCAAs content and specifically the Leucine content. [11] In 1992 Nair *et al*, reported the positive effect of leucine, a BCAA, on stimulating anabolism in the resting skeletal muscle.[23] Stimulation of protein anabolism by leucine was later explained by its stimulation of mTOR signalling.[24] Leucine stimulates protein anabolism in a "dose-dependent" manner, to the extent that the leucine content of a meal has been proposed to measure a meal's capacity to stimulate muscle protein synthesis .[25] in this study, we sought to examine the effect of the content of BCAAs on protein anabolism.

Patients who received BCAAs enriched WP formula (Group I) had significantly higher %Δ ALB despite the higher %Δ CRP, which reflects hyper catabolism, indicating a positive shift in protein metabolism favoring anabolism. This was further indicated by the significantly lower percentage changes in blood urea nitrogen (%ΔBUN) in Group I compared with Group II with Mean difference±SEM of -4.44%±6.36%. In summary, BCAAs enriched WP formula was superior to standard WP formula in stimulating ALB synthesis and LBM anabolism/catabolism ratio in cachexic hospitalized hypoalbuminemic patients. This study is limited by its retrospective design and its use of single-center data. However, our center is an experienced and high-volume unit, so our data may be useful to other centers. A larger, multisite prospective study is required to establish the effect of BCAA dose on stimulating protein synthesis.

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