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Research Article
Efficacy of a High Protein Oral Nutritional Supplement in Maintenance Hemodialysis Patients

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Abstract

Background and Objective: Protein energy wasting (PEW) with hypoalbuminemia is common in Chronic Kidney Disease (CKD). Dialysis patients may benefit from high protein (HP) supplementation. The aim of the present study was to investigate a high protein oral nutritional supplement (ONS) (intervention) that suitable for hemodialysis patient compared to an existing ONS formulated for CKD patients on maintenance hemodialysis (MHD) (control) in increasing serum albumin in hypoalbuminemic patients with similar recommended energy intake. **Materials and Methods:** This single-center prospective, randomized, open-label, controlled, parallel group study investigated patients on stable thrice-weekly MHD receiving either daily one or two bottles of intervention ONS or a control ONS for 8 weeks. Of 76 randomized patients, 68 were analysed. Dietary evaluation and individualized dietetic prescription was applied. Serum albumin, anthropometry, blood chemistry, hematology, vital signs and adherence were measured. **Results:** Both groups significantly increased ($p<0.001$) energy and macronutrient intake from baseline, resulting in comparable within-group increases in body weight and Body Mass Index (BMI) by week 8 ($p<0.05$). The intervention group had superior improvements in serum albumin compared to controls (group mean difference (95% CI) baseline to week 4 = 2.11 (0.51; 3.71) g/L and to week 8 = 2.25 (0.69; 3.81) g/L). The intervention group also had increased pre-albumin and total protein levels after 4 and 8 weeks ($p<0.05$ vs baseline). **Conclusion:** Post-dialysis blood urea nitrogen remained stable. The intervention group had increased hemoglobin, improved red cell morphology and lower hs-CRP. Adherence was >99% in both groups. There were no reports of gastrointestinal intolerance. The increase in serum albumin over time was more prominent in the intervention ONS group vs controls.

Key words: Oral nutritional supplement, hypoalbuminemia, nutritional status, energy intake, high protein supplement, hemoglobin

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Prevalence reporting of protein energy wasting (PEW) in CKD patients on MHD ranges between 36 and 74%[1,2]. The pathophysiology of PEW is complex and multiple factors play a role[3,4] including anorexia, dietary restrictions, dialysis-related nutrient losses, dialysis adequacy, underlying inflammatory state, altered substrate metabolism and gastrointestinal symptoms, among others. Standard anthropometric indicators of malnutrition are challenging in CKD due to the difficulties in successfully determining edema-free body weight or the requirement for technical devices[5]. Instead, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline, serum albumin level is a simple and sensitive indicator of PEW and correlates with inflammatory proteins such as C-Reactive Protein (CRP)[5-7]. Both of these parameters are of prognostic importance[8]. Anthropometric indicators also define PEW in CKD patients[9]. Both PEW and hypoalbuminemia are associated with a higher risk of infectious complications, hospitalization and lower survival in CKD[8,10]. Additionally, albumin and PEW are also linked to anemia in MHD patients[11].

Therefore, correction of hypoalbuminemia is of clinical interest in CKD. Firstly, because it is indicative of restored nutritional status[5,6]. Secondly, improved serum albumin enhances responsiveness to treatment of other clinically relevant markers, such as hemoglobin[11]. Thirdly, even small improvements in serum albumin levels alter prognosis in patients with End-Stage Renal Disease (ESRD)[12]. This comparative non-inferiority study aimed to investigate the effectiveness of a HEHP intervention ONS indicated for chronic wasting with hypoalbuminemia on serum albumin levels, dietary intake and nutritional status in MHD patients at risk of PEW.

MATERIALS AND METHODS

Study area: The study was carried out from March 2022 to July 2022. This study was carried out in nursing house of Chung Shan Medical University Hospital.

Study design: The trial was a randomized, open-label, parallel group non-inferiority trial of the efficacy of a HEHP ONS (intervention) vs a disease-specific ONS (control) in improving nutritional status and serum albumin in CKD patients on MHD. This study screened and randomized 76 adult hemodialysis patients requiring nutritional supplementation for dietary intake below recommended levels combined with hypoalbuminemia and finally included 68 patients who were selected from a single dialysis center in Taiwan over 7 months. To qualify for inclusion, patients had to be on regular intermittent hemodialysis three times weekly for 3.5-4.5 hrs per session and have at least one of the following indicators of malnutrition: Plasma albumin level less than 38 g/L (according to local laboratory reference range), energy intake of less than 35 kcal/kg Ideal Body Weight (IBW) per day or protein intake of less than 1.2 g/kg IBW per day. Exclusion criteria included Body Mass Index (BMI) <18.5 kg/m^2 with energy intake not meeting 50% of the recommended requirement (in order to reduce large nutritional status deviations among the small study sample), BMI >30 kg/m^2, abnormal liver function, malignancy, infectious disease, post-operative status, surgery or hospitalization scheduled for the upcoming month, gastrointestinal disease or impaired function, bowel obstruction, pregnancy or lactation, poor tolerance of nutritional supplements, acute condition with multiple organ failure, palliative care or expectation of poor study compliance.

Eligible patients who had given consent to be included in the trial were randomized either to the intervention group where they received Fresubin® Protein Energy Drink (Fresenius Kabi) or to a control group who received NEPRO with CARBSTEADY® (Abbott Nutrition). The NEPRO with CARBSTEADY® is a high energy, high protein, reduced electrolyte nutritional supplement indicated for therapeutic nutrition support of CKD patients on MHD. Fresubin® Protein Energy Drink is a high energy, high protein ONS intended for use in patients with chronic wasting conditions or hypoalbuminemia. Since this product indication was consistent with the features of PEW, in Taiwan the intervention ONS is used as a disease-specific product exclusively for hemodialysis patients. The intervention was from September 2020 to December 2021.

Nutrition supplementation protocol: Background nutrition from normal dietary intake used NKF-KDOQI recommendations[13] with reference to the nutritional status of each patient. Target calories were 30-35 kcal/kg per day and the daily protein target was 1.2-1.4 g/kg. The diet was supplemented with ONS according to each patient's requirement as follows: Patients in the intervention group consuming $\geq$75% of recommended energy requirements from normal diet alone received one bottle (200 mL, providing 300 kcal and 20 g protein) of the intervention ONS per day, while those taking <75% of recommended energy intake received two bottles of the intervention drink per day. Patients in the control group consuming $\geq$75% of recommended energy requirements received two cans (237 mL, providing

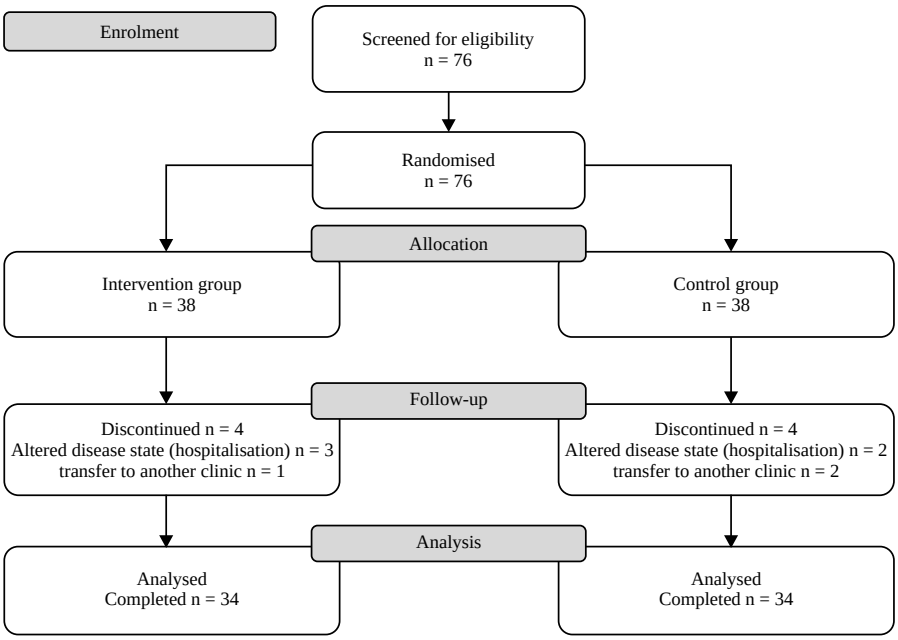

Fig. 1: CONSORT diagram for subject disposition

425 kcal and 19 g protein) every three days, while those taking <75% of recommended energy requirement from normal diet received four units of the product every three days. These regimens were designed to provide almost isocaloric nutritional intake compensating for the differing volumes and nutritional content of the two ONS products being compared. All patients who completed the study continued the nutrition supplementation protocol for 8 weeks. See CONSORT Fig. 1 for patient disposition.

Data collection protocol: Baseline data consisted of demographics, medical history, vital signs, anthropometric assessment (body weight, BMI, mid-arm circumference, mid-arm muscle circumference, skinfold thickness and waist-to-hip ratio using standardized techniques), standard blood biochemistry and electrolytes, serum lipid profile, plasma proteins, selected inflammatory markers, organ function tests and complete blood count. Nutritional requirements were calculated for each patient and a 3-day diary recall was completed by each patient (for 2 weekdays including a dialysis day and a weekend day) and analyzed. Gastrointestinal symptoms were recorded. Measurements were repeated after 4 weeks of nutrition supplementation and again after 8 weeks (study completion). Patients were contacted weekly by telephone to check ONS consumption and calculate adherence to nutritional prescriptions.

Ethical considerations: The study was conducted in accordance with the current version of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines with reference to a study protocol approved by the Institutional Review Board of the Chung Shan Medical University Hospital (Approval number CS2-20011). Each subject signed informed consent before trial inclusion.

Statistical methods and analysis: The primary outcome variable was improvement in nutritional status measured as a change in serum albumin levels between baseline and week 8, while secondary analysis was a change in the same parameter at week 4. The null hypothesis was that the group difference (test minus control) in an estimated change in serum albumin levels between baseline and week 8 would be $\leq$-2 g/L, where the non-inferiority margin was taken as -2 g/L. For the sample size calculation, a standard deviation of 0.3 g/dL for the mean change in serum albumin from baseline to week 8 in both groups was assumed. Further, the true difference in the primary endpoint between the test and control group was set to -0.05 as worst case scenario. In order to obtain a power of 90%, 32 evaluable patients per group were needed. Overall, a total of 76 patients (38 per group) were enrolled to account for a drop-out rate of 15%. Continuous data are shown as Mean$\pm$SD, categorical data as absolute and relative frequency (%). The primary endpoint was analyzed via Analysis of Covariance (ANCOVA) with baseline albumin level as covariate in order to compare the change in serum albumin after 8 weeks between groups. Change in serum albumin after 4 weeks was analyzed in a separate ANCOVA. Secondary endpoints were analyzed in separate

ANCOVAs per time point. Repeatedly measured data that were normally distributed were analyzed via One Way Repeated Measure Analysis of Variance (ANOVA) to assess the change between timepoints within one group. For all analysis, statistical significant was taken as a p-value of less than 0.05 ($p<0.05$). Statistical analysis of the data was performed using Statistics Package for Social Science software (SPSS version 18.0 for windows; SPSS Inc., Chicago).

RESULTS

Patients: In total, 76 patients were screened for eligibility and subsequently randomized in a 1:1 ratio between intervention and control groups resulting in 38 patients per group. Among the intervention group, 4 patients discontinued the study due to hospitalization (3 patients) and transfer to a different dialysis clinic (1 patient). Four control patients also discontinued the trial due to hospitalization (2 patients) and clinic transfer (2 patient) (Fig. 1).

Baseline demographics and clinical status for the two groups were shown in Table 1. Groups were comparable with respect to baseline variables.

Nutritional intake: At baseline, all included patients were failing to meet the KDQOI-recommended nutritional intake of energy and protein. At baseline, the mean energy intake of patients in the intervention group was 1187±133 kcal/day (21.6±2 kcal/kg IBW/day) and the mean protein intake was 53.0±8.4 g/day (0.96±0.11 g/kg IBW/day), while mean energy and protein in the control group were 1246±169 kcal/day (21.9±2.9 kcal/kg IBW/day) and 54.2±9.9 g/day (0.95±0.17 g/kg IBW/day) respectively. Mean±SD values were comparable between groups. Based on these assessments of dietary intake adequacy, 26 (76%) patients in the intervention group and 24 (71%) patients in the control group did not meet 75% of required intake, while the remainder met at least 75% of recommended intake. The ONS was prescribed accordingly. Supplementation continued for a similar duration of 58±3 days in the intervention group and 58±2 days in the control group.

As a result of ONS, both groups had significant increases ($p<0.001$) in energy, protein, fat and carbohydrate intake from baseline to week 4, which were sustained at week 8. Intake improved such that patients in both groups met target intake levels for protein, but neither group met the minimum energy target of 30 kcal/kg/day (Table 2).

Serum albumin and plasma proteins: Table 3 shows the results of ONS on the primary outcome variable of serum week 4 and at week 8 compared to baseline in the intervention group, while in controls the increase from baseline was only significant at week 8. However, neither group achieved normal levels of albumin during the study, according to the specified cut-off of 38 g/L. In fact, both groups fell short of achieving normoalbuminemia by this criterion, although achieving normoalbuminemia was not the goal of the study due to the relatively short intervention period. At week 8, the estimated mean group difference in change from baseline in serum albumin amounted to 3.35 g/L, 95% CI = [0.69; 3.81]. Since the lower limit of the 95% CI fell above the non-inferiority margin of 2 g/L, non-inferiority was demonstrated. The 95% CI was completely above 0 g/L, such that the intervention ONS was found to be superior to the control ONS at both week 4 and week 8 (Table 3).

Group difference in change from baseline was statistically significant for pre-albumin at week 4 (28.80 mg/L 95% CI = 4.47; 55.10, $p = 0.022$) (Table 3). There were no other significant intra- or inter-group changes in any of the serum protein markers from baseline. However, subgroup analysis for dose effect found that the subgroup of patients who received 2 bottles daily ($n = 26$) compared to those who received 1 bottle ($n = 8$) of intervention ONS had significantly higher serum albumin levels at week 4 (36.8±2.6 g/L vs 31.9±4.8 g/L, $p = 0.011$) and week 8 (37.9±3.1 g/L vs 31.9±4.1 g/L, $p = 0.001$). The same result was found for pre-albumin levels within the intervention group receiving different doses at week 4 (293.1±63.3 mg/L vs 226.0±61 mg/L, $p = 0.046$) and week 8 (303.0±71.1 mg/L vs 226.0±65.4 mg/L, $p = 0.036$) respectively. In the controls, no dose effect on serum proteins was found. While hs-CRP in both groups was in the normal range throughout, this marker was significantly reduced over the study in the intervention group, but not in controls. Results showed a significant fall from a baseline of 2.1±2.1 mg/dL to 1.3±2.7 mg/dL at week 4 ($p = 0.011$) and 0.96±1.3 mg/dL at week 8 ($p = 0.01$ vs baseline) in the intervention group.

Anthropometry: The ONS resulted in small but statistically significant improvements in anthropometric indicators in both groups (Table 4). In the intervention group, body weight and BMI increased significantly from baseline to week 4 and the increase was sustained to week 8. In the controls, there was no difference in body weight or BMI between baseline and week 4, but significant increases were observed at week 8 compared to baseline. Mid-arm circumference (MAC) and mid-arm muscle circumference (MAMC) increased in the controls, while hip circumference was significantly higher in the intervention group at week 8 compared to baseline.

Table 1: Baseline demographic and clinical status variables

Parameter	Intervention group (n = 34)	Control group (n = 34)	p-value
Male n (%)	13 (38)	17 (50)	NS
Female n (%)	21 (62)	17 (50)	NS
Age (years) Mean±SD	69.0±7.4	69.4±8.4	NS
Comorbidities n (%)			NS
Diabetes	21 (62)	19 (56)	
Hypertension	22 (65)	20 (59)	
Stroke	2 (6)	3 (9)	
Coronary artery disease	9 (26)	7 (21)	
Glomerulonephritis	6 (18)	8 (24)	
Hyperlipidemia	1 (3)	2 (6)	
Heart failure	1 (3)	2 (6)	
Lupus erythematosus	1 (3)	0 (0)	
Chronic obstructive pulmonary disease	1 (3)	0 (0)	
Vital signs Mean±SD			
Systolic blood pressure (mmHg)	137.9±16.7	130.2±26.4	NS
Diastolic blood pressure (mmHg)	68.0±9.5	69.8±5.3	NS
Heart rate (bpm)	78.2±8.8	75.8±3.6	NS
Breath rate (bpm)	19.2±1.4	18.2 ±1.0	NS
Temperature (°C)	36.4±0.2	36.4±0.2	NS
Body weight (kg) Mean±SD	56.5±8.3	56.2±8.6	NS
Body mass index (kg/m^2) Mean±SD	22.8±4.6	21.7±3.7	NS

SD: Standard deviation, NS: Not significant, mmHg: Millimeters mercury and bpm: Beats/breaths per minute

Table 2: Nutritional intake parameters

	Intervention group (n = 34) Mean±SD			Control group (n = 34) Mean±SD		
Parameter	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
Energy (kcal/day)	1187±133	1603±175*	1609±172*	1246±169	1624±134*	1625±134*
Energy (kcal/kg/day)	21.6±2	29.0±1.8*	29.2±1.7*	21.9±2.9	28.5±3.1*	28.5±3.1*
Protein (g/day)	53.0±8.4	75.6±6.9*	76.1±7.3*	54.2±9.9	74.4±6.6*	74.8±6.8*
Protein (g/kg/day)	0.96±0.11	1.37±0.06*	1.38±0.05*	0.95±0.17	1.30±0.09 *	1.31±0.09*
Fat (g/day)	39.6±6.2	56.0±4.1*	56.4±3.8*	42.4±7.1	56.3±4.1*	56.7±4.0*
Carbohydrate (g/day)	154.7±26.5	199.1±32.5*	199.0±32.0*	161.8±26.5	204.9±27.1*	204±27.0*

SD: Standard deviation, kcal: Kilocalories, g: Grams and *p<0.001 vs baseline within group

Table 3: Serum albumin, total protein, pre-albumin and transferrin in the subjects during intervention

	Mean±SD		Estimated mean group difference in change from baseline (95%CI)[#]	
Parameter	Intervention group (n = 34)	Control group (n = 34)	Week 4	Week 8
Albumin (g/L)				
Baseline	33.1±4.0	33.2±4.2	2.51 (0.51; 3.71)	3.35 (0.69; 3.81)
Week 4	35.6±3.8*	33.7± 4.9		
Week 8	36.4±4.2*	34.4±4.3[#]		
Total protein (g/L)				
Baseline	64.0±7.1	64.3±4.9	1.34 (-1.06; 3.74)	0.72 (-1.52; 2.95)
Week 4	67.0±6.9	65.9±5.3		
Week 8	66.4±5.8	65.9±5.2		
Pre-albumin (mg/L)				
Baseline	248.5±65.2	242.0±69.4	28.80 (4.47; 55.10)	36.41 (-7.05; 51.86)
Week 4	277.3±68.3	242.8±74.1		
Week 8	284.9±76.4	257.2±86.1		
Transferrin (mg/dL)				
Baseline	169.8±42.0	154.5±30.1	5.97 (-5.88; 17.81)	5.61 (-5.38; 16.60)
Week 4	178.0±43.4	159.9±30.5		
Week 8	180.0±46.6	161.2±27.9		

*p<0.001 vs baseline, [#]p = 0.043 vs baseline, SD: Standard deviation, CI: Confidence interval and [#]group difference = intervention-control, results are from ANCOVA with baseline values as covariate

Table 4: Anthropometric parameters of the subjects during the intervention

	Intervention group (n = 34) Mean±SD			Control group (n = 34) Mean±SD		
Parameter	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
Body weight (kg)	56.5±8.3	57.1±8.1*	57.3±8.0*	56.2±8.6	56.3±8.0	56.6±8.1[#]
BMI (kg/m^2)	22.8±4.6	23.0±4.5*	23.10±4.5*	21.7±3.7	21.8±3.5	21.9±3.5[#]
MAC (cm)	28.1±3.8	28.3±3.7	28.3±3.8	27.0±2.5	27.1±2.5[§]	27.4±2.5[#]
MAMC (cm)	22.5±3.3	22.7±3.3	22.7±3.2	21.9±2.6	22.0±2.5	22.3±2.7[#]
Triceps skinfold (mm)	17.9±5.0	17.9±5.0	17.8±4.5	16.3±5.8	16.4±5.6	16.5±5.3
Waist circumference (cm)	81.5±7.9	81.5±7.8	81.6±7.6	84.0±6.2	84.1±5.9	84.0±5.7
Hip circumference (cm)	87.5±4.8	87.7±4.9	87.9±4.8*	88.3±5.2	88.3±5.5	88.3±5.5
Waist-to-hip ratio	0.93±0.07	0.93±0.06	0.93±0.06	0.95±0.06	0.95±0.06	0.95±0.06

BMI: Body mass index, MAC: Mid-arm circumference, MAMC: Mid-arm muscle circumference, cm: Centimeters, mm: Millimeters, *p<0.001 vs baseline, within group, [#]p<0.05 vs baseline, within group and [§]p<0.05 vs week 8, within group

Table 5: Hematology and iron status

	Intervention group (n = 34) Mean±SD			Control group (n = 34) Mean±SD		
Parameter	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
Hemoglobin (g/dL)	9.4±1.1	9.6±1.2	9.8±1.2[§]	10.0±1.0	9.9±1.2	9.8±1.2
Mean cell volume (fl)	95.7±5.1	96.7±5.1	97.9±5.5*	92.6±6.6	93.0±7.3	93.4±7.6
Mean cell hemoglobin (pg)	31.0±1.6	31.6±1.7[#]	31.9±1.7*	30.8±2.6	30.8±2.9	31.1±2.9[§]
TIBC (ug/dL)	230.7±40.1	250.6±48.8*	242.7±48.8*	205.0±41.5	207.6±43.7	219.0±35.7*

TIBC: Total iron binding capacity, SD: Standard deviation, [§]p = 0.029, *p<0.03 vs baseline, within group, [#]p = 0.008 vs baseline and p = 0.032 vs week 8 and [§]p = 0.002 vs week 4

Covariate analysis did not reveal an inter-group difference in the change in body weight from baseline to week 4 [mean difference (95% CI) = 0.232 (-0.14; 0.605), p = 0.217] or week 8 [(mean difference (95% CI) = 0.059 (-0.413; 0.531), p = 0.803]. Neither was there a group difference in change in BMI from baseline to week 4 [mean difference (95% CI) = 0.09 (-0.058; 0.239), p = 0.227] or week 8 [mean difference (95% CI) = 0.043 (-0.145; 0.231), p = 0.653].

Blood chemistry and metabolic indicators: There were no differences from for baseline any serum electrolyte, including serum phosphate and potassium, liver function or metabolic indicators including blood glucose, HbA1c or serum lipid fractions for either group (see supplementary Table S1 for data values). Only the intervention group showed a significant increase in serum calcium levels at week 8 (9.1±1.2 mg/dL vs baseline 8.6±1.0 mg/dL, p = 0.008 and vs week 4 8.8±1.1 mg/dL, p = 0.002)), although values were within the normal reference range. The intervention group also had significantly decreased LDH levels over the course of the study (baseline 232.1±90.3 U/L; week 4 204.5±54.0 U/L, p = 0.045 vs baseline; week 8 196.1±48.1 U/L, p = 0.001 vs baseline). This was not seen in the control group.

Hematology and iron status indicators: There were no intra-group changes in the hematological indicators red blood cells, white blood cells, platelets and hematocrit following nutritional supplementation. Neither was there a group difference in these parameters (see supplementary Table S2 for data values). However, hemoglobin levels increased significantly at week 8 in the intervention group, but not in controls (Table 5).

Mean cell volume increased significantly between baseline and week 8 in the intervention group. Mean cell hemoglobin (MCH) progressively increased from baseline to week 4 and week 8 only in the intervention group. In the control group, a statistically significant rise in MCH was found between week 4 and week 8 only. Total Iron Binding Capacity (TIBC) increased at week 4 compared to baseline in the intervention group. In both groups, there was a significant increase in TIBC at week 8 compared to baseline.

Renal chemistry: Patients in both groups had significantly higher pre-dialysis blood urea nitrogen (BUN) levels by week 8 of the study and between baseline and week 4 in the intervention group. Post-dialysis BUN, however, remained statistically similar throughout the study and within normal limits. Creatinine levels remained the same throughout (Table 6).

Safety and compliance: Vital signs remained unchanged at week 4 and week 8 compared to baseline in both groups

Table 6: Pre- and post-dialysis renal chemistry

	Intervention group (n = 34) Mean±SD			Control group (n = 34) Mean±SD		
Parameter	Baseline	Week 4	Week 8	Baseline	Week 4	Week 8
Pre-dialysis BUN	70.2±16.3	85.1±23.8*	79.8±21.7*	65.3±18.0	65.8±19.8	72.8±21.5*
Post-dialysis BUN	18.7±8.1	20.3±5.6	19.3±7.2	17.3±5.8	17.8±6.2	19.5±7.0
Pre-dialysis creatinine	6.3±1.9	6.7±1.9	6.6±1.5	8.5±2.3	8.2±2.5	8.5±2.5
Post-dialysis creatinine	2.2±0.9	2.2±0.5	2.1±0.6	2.9±0.9	2.9±0.9	3.0±1.0

BUN: Blood urea nitrogen, SD: Standard deviation and *p<0.05 vs baseline within group

(supplementary Table S3 for data values). There were no reports of gastrointestinal symptoms. Adherence was equally high in both groups (99.8±0.7% in controls vs 99.8±0.4% in the intervention group, NS).

DISCUSSION

This study investigated the effect of 8 weeks of HEHP ONS in hypoalbuminemic MHD patients with insufficient energy and protein intake according to KDOQI recommended targets. Compared to a control ONS routinely used in Taiwan for such patients, the intervention product was non-inferior with respect to the pre-defined non-inferiority margin in efficacy and safety profile. The study shows high protein content even superiority with respect to the primary endpoint was demonstrated despite similar improvements in energy and other macronutrient intakes and increases in anthropometric indicators. Use of both ONS products brought protein intake up to prescribed target levels to meet KDOQI recommendations with the intervention group receiving 1.38±0.05 g/kg daily by week 8 and the control group 1.31±0.09 g/kg per day. Energy intake was significantly improved in both groups although falling slightly short of the 30 kcal/kg target intake (intervention group 29.2±1.7 kcal/kg at week 8; control group 28.5±3.1 kcal/kg at week 8). Both groups still achieved well above the KDOQI target of 25 kcal/kg/day[5].

An ONS dose-effect was also found, with higher doses associated with improved albumin and pre-albumin levels only in the intervention group. This may be explained by a higher BMI in the intervention group indicating better nutritional status and therefore enhanced responsiveness to ONS. Also importantly, the protein type provided in the two products could explain the differential impact on serum albumin, since the control product is mainly caseinate. It has previously been demonstrated that the serum albumin response to caseinate-based protein is lower than for other milk protein forms[14].

The intervention group had improved hemoglobin and red cell morphology and lower inflammatory hs-CRP and LDH levels after 8 weeks. These results occurred without deviations from baseline in serum electrolytes, or metabolic indicators despite significant increases in carbohydrate and fat intake. As a result of significantly higher protein intakes, both groups developed higher pre-dialysis BUN levels but post-dialysis BUN measures were stable compared to baseline and within normal ranges. Therefore, the use of the intervention ONS not only raised protein intake to target levels but produced better results for measures of anemia, inflammation and tissue damage[15].

Dietary management of CKD is complex. Renal diets are typically restrictive. Additionally, CKD patients have risks for disease-related malnutrition, as well as adverse health events related to underlying morbidities and secondary metabolic complications[3,4,16-18]. Compared to the highly restrictive diets necessary for metabolic control of conservatively managed CKD patients, dietary prescriptions in MHD patients are more liberal in terms of protein, fluid and electrolyte intake[5]. This is necessary because dialysis increases nutritional requirements due to additional nutrient losses, inflammatory responses, dialysis-related anorexia and hypermetabolism, on top of the unfavorable hormonal and metabolic environment of End-Stage Renal Disease (ESRD)[3]. Medical nutrition therapy in patients who cannot achieve optimal oral intake includes ONS[5]. The current study indicates that, for patients with hypolbuminemia but normal BMI, general improvements in protein and energy intake using ONS produce positive serum albumin responses and anthropometry. This occurred without a negative impact on serum electrolytes or other metabolic markers.

The intervention ONS is indicated for hypoalbuminemia and chronic wasting diseases and proved to be effective in increasing serum albumin and other serum protein markers. Serum albumin was not corrected to normal (defined as >38 g/L in this study) with this intervention despite increased protein intake of >20 g per day together with a >400 kcal increment in energy. Possibly the supplementation period was too short given the dynamics of serum albumin in MHD and the low baseline level.

Low serum albumin is a clinical concern in MHD patients. For nutrition assessment it is a sensitive surrogate for PEW risk[7] in CKD patients, correlating with indicators such as MAMC and skinfold thickness[9]. This is relevant due to the practical difficulties in obtaining accurate edema-free ("dry") body weight and therefore accurate BMI assessments in MHD patients[5]. In this study mean BMI remained normal in both groups. Rather, it was hypoalbuminemia and low dietary intake that indicated nutritional risk.

Low albumin is a predictor of clinical outcomes including hospitalization and survival[8,10]. Therefore, the intervention ONS was associated with superior clinical benefits since serum albumin was significantly increased after 4 weeks of supplementation and to a greater degree than the increase achieved in the controls. The differential increase in albumin exceeded 2 g/L, which is large enough to change mortality risk in a dialysis patient with otherwise similar comorbid or demographic characteristics[12]. An even greater mean increase (>4 g/L) in the intervention group was detected after 8 weeks in patients who received a higher dose (2 bottles per day) ONS, along with the same finding for pre-albumin levels-another strong marker for both PEW and clinical outcome[12]. An eight-months retrospective study showed that ONS provided better survival and reduced missed dialysis treatment, however, albumin was lower for ONS patients[19]. Albumin, dry weight and triceps skinfold thickness significantly increased during six-months intervention[20]. The short-term intervention of this study is only 8 weeks compared with the previous study, which reveals the high efficiency of protein supplementation. This is an important result because it demonstrates that improved plasma protein status is actionable via nutrition intervention within a matter of weeks. With a longer duration of ONS, anthropometric changes could be further improved.

Both albumin and pre-albumin levels are associated with inflammation, which is a factor in nutritional risk[3]. An inflammatory state is common in MDH and is also of prognostic value[8,21]. While albumin and pre-albumin levels rose in the intervention group, hs-CRP levels, although normal, fell significantly. A proportion of the deviation in serum albumin in CKD is due to CRP and albumin adjusted for CRP is associated with poorer survival outcomes in CKD patients[8]. The finding of this study that the malnutrition-inflammation complex is responsive to optimization of energy and protein intake via ONS is evidence that nutritional care is consistent with overall good clinical management of CKD[22].

Factors that improve serum albumin in MHD patients may also improve Hemoglobin (Hb)[11] as has been shown in this study. The CHOIR trial[23,24] classically showed that attempts at driving Hb correction with erythropoeitic agents may not be beneficial because the response is modified by nutritional status[25,26]. Novel modelling techniques have shown that maximal Hb corrections occur when serum albumin is in the normal reference range, while low albumin may be associated with an up to 70% reduction in response in anaemic CKD patients[11]. Concurrent use of erythropoietin (EPO) was unknown in this study, although baseline mean Hb values were below the threshold for EPO use[27]. The degree of the small but statistically significant increases in Hb and improvements in red cell morphology seen in the intervention group appear indicative of a response to optimized energy and protein intake and possibly the 50% higher iron content of the intervention ONS compared to the control. This is supported by results showing a significant increase in TIBC[28].

The significant increase in protein intake in both groups raised pre-dialysis BUN levels, as would be expected. However, post-BUN levels remained unchanged throughout and there were no other safety or tolerance concerns associated with the ONS either in blood test results or related to gastrointestinal symptoms. Compliance with ONS use in both groups was close to perfect, indicating high acceptability by patients.

CONCLUSION

In this investigation, the efficacy of the intervention ONS was found to be similar to the control ONS in terms of improvements in dietary intake parameters and nutritional status of CKD MHD patients, without associated unwanted effects of deranged serum chemistry. While sub-optimal energy and protein intake was improved over 8 weeks in both study groups, the intervention ONS was found to be superior in raising serum albumin levels in this hypoalbuminemic patient group compare to control product. The intervention group also benefited from improved hemoglobin and mean cell volume. Adherence to the renal drink was very high indicating high acceptability to patients. In summary, the intervention ONS provided important clinical benefits to nutritionally at-risk end-stage CKD patients on hemodialysis without any safety concerns.

SIGNIFICANCE STATEMENT

The purpose of the present study was to investigate a high protein oral nutritional supplement that suitable for hemodialysis patient. The intervention showed increased hemoglobin, improved red cell morphology and lower hs-CRP. This study was to investigate a high protein oral nutritional supplement that suitable for hemodialysis patient compared

to an existing ONS formulated for CKD patients on maintenance hemodialysis in increasing serum albumin in hypoalbuminemic patients with similar recommended energy intake. After intervention, the increased hemoglobin, improved red cell morphology and reduced hs-CRP were significantly found.

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Table S1: Biochemical analyses during the intervention

Parameter	Baseline	Week 4	Week 8
Blood glucose (mg/dL)			
Control group (n = 34)	166.0±70.0	163.6±80.0	165.6±63.1
Intervention group (n = 34)	168.6±65.7	166.1±81.1	160.9±55.4
HbA1C (%)			
Control group (n = 34)	6.3±1.6	6.5±1.7	6.5 ±1.7
Intervention group (n = 34)	6.2±1.2	6.2±1.2	6.3±1.4
Cholesterol (mg/dL)			
Control group (n = 34)	133.3±35.1	133.2±31.7	132.7±33.0
Intervention group (n = 34)	141.4±39.6	144.7±37.4	144.7±34.0
Triglyceride (mg/dL)			
Control group (n = 34)	128.7±87.3	112.9±55.3	111.7±54.7
Intervention group (n = 34)	145.7±61.0	144.3±68.5	148.9±72.5
HDL (mg/dL)			
Control group (n = 34)	40.5±10.8	41.7±11.7	41.9±12.5
Intervention group (n = 34)	38.9±16.4	40.8±11.6	41.1±13.4
LDL (mg/dL)			
Control group (n = 34)	69.2±24.4	71.7±23.1	69.8±22.6
Intervention group (n = 34)	72.5±33.3	76.2±31.5	73.3±31.4
GOT (IU/L)			
Control group (n = 34)	18.1±4.8	18.7±4.4	18.4±6.9
Intervention group (n = 34)	24.4±9.9	23.0±8.8	24.7±8.8
GPT (IU/L)			
Control group (n = 34)	13.8±6.2	15.2±6.2	15.6±7.8
Intervention group (n = 34)	21.2±16.6	19.2±13.3	21.2±12.5
Total bilirubin (mg/dL)			
Control group(n = 34)	0.5±0.4	0.5±0.3	0.5±0.3
Intervention group(n = 34)	0.3±0.3	0.3±0.2	0.3±0.2
LDH (U/L)			
Control group (n = 34)	174.2±37.9	181.5±57.1	179.6±53.3
Intervention group (n = 34)	232.1±90.3	204.5±54.0$	196.1±48.1§
CPK (U/L)			
Control group (n = 34)	75.0±60.7	83.1±75.4	90.8±81.8
Intervention group (n = 34)	52.7±59.3	68.1±35.9	73.1±38.8
Uric acid (mg/dL)			
Control group (n = 34)	6.3±1.5	5.9±1.0	6.3±1.3
Intervention group (n = 34)	6.3±1.8	6.2±2.0	5.8±1.6
Calcium (mg/dL)			
Control group (n = 34)	9.1±0.8	9.3±0.7	9.0±0.8
Intervention group (n = 34)	8.6±1.0	8.8±1.1*	9.2±1.2#
Sodium (mmol/L)			
Control group (n = 34)	136.1±3.6	136.3±3.2	136.1±3.1
Intervention group (n = 34)	137.3±5.2	135.7±4.4	136.4±3.6
Potassium (mmol/L)			
Control group (n = 34)	4.6±0.9	4.4±0.9	4.5±0.8
Intervention group (n = 34)	4.3±0.8	4.6±0.7	4.5±0.7
Phosphate (mg/dL)			
Control group (n = 34)	4.4±1.2	4.1±1.3	4.3±1.0
Intervention group (n = 34)	4.2±1.1	4.5±1.3	4.5±1.2

Table S1: Continue

Parameter	Baseline	Week 4	Week 8
Magnesium (mg/dL)			
Control group (n = 34)	2.5±0.3	2.5±0.3	2.5±0.4
Intervention group (n = 34)	2.3±0.4	2.5±0.6	2.4±0.4
Iron (ug/dL)			
Control group (n = 34)	55.2±23.3	55.7±16.8	54.5±18.5
Intervention group (n = 34)	54.9±23.7	57.1±27.6	57.4±21.3
Chloride (mmol/L)			
Control group (n = 34)	98.4±3.1	98.1±2.8	97.1±3.1
Intervention group (n = 34)	98.8±5.3	98.0±4.1	98.8±3.4

*p = 0.002 vs baseline, #p = 0.008 vs baseline, $p = 0.045 vs baseline, §p = 0.001 vs baseline, all other changes are not statistically significant, HDL: High density lipoprotein, LDL: Low density lipoprotein, GOT: Glutamic oxaloacetic transaminase, GPT: Glutamic pyruvic transaminase, LDH: Lactate dehydrogenase and CPK: Creatine phosphokinase

Table S2: Serum hematology during the intervention

Parameter	Baseline	Week 4	Week 8
Red blood cells (×10^6/uL)			
Control group (n = 34)	3.3±0.4	3.2±0.5	3.2±0.5
Intervention group (n = 34)	3.0±0.3	3.1±0.4	3.1±0.4
White blood cells (×10^3/uL)			
Control group (n = 34)	6.8±2.2	7.2±2.2	6.7±1.9
Intervention group (n = 34)	8.1±2.2	7.8±2.1	7.6±1.6
Platelets (×10^3/uL)			
Control group (n = 34)	178.2±56.2	177.8±57.5	177.4±64.6
Intervention group (n = 34)	210.9±94.8	196.7±69.3	197.8±70.1
Hematocrit (%)			
Control group (n = 34)	30.0±2.9	29.9±3.4	29.6±3.7
Intervention group (n = 34)	28.9±3.2	29.4±3.4	30.2±3.6
Mean cell hemoglobin concentration (g/dL)			
Control group (n = 34)	33.3±1.0	33.1±1.1	33.2±1.0
Intervention group (n = 34)	32.4±1.0	32.7±1.0	32.6±1.2

All changes are not statistically significant

Table S3: Vital signs during the intervention

Parameter	Baseline	Week 4	Week 8
Temperature (°C)			
Control group (n = 34)	36.4±0.2	36.4±0.2	36.4±0.2
Intervention group (n = 34)	36.4±0.2	36.4±0.3	36.4±0.2
Blood pressure (mmHg)			
Systolic			
Control group (n = 34)	130.2±26.4	128.0±17.4	127.7±13.9
Intervention group (n = 34)	137.9±16.7	137.5±20.4	136.6±16.7
Diastolic			
Control group (n = 34)	69.8±5.3	68.9±8.3	69.3±6.4
Intervention group (n = 34)	68.0±9.5	68.7±10.6	69.4±7.3
Heart rate (beats per minute)			
Control group (n = 34)	75.8±3.6	75.9±4.3	75.9±4.3
Intervention group (n = 34)	78.2±8.8	78.2±8.5	78.2±8.3
Respiratory rate (breaths per minute)			
Control group (n = 34)	18.2±1.0	18.4±0.9	18.3±1.0
Intervention group (n = 34)	19.2±1.4	19.2±1.8	19.1±1.5

All changes are not statistically significant