Clinical Nutrition ESPEN 25 (2018) 68–77

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Clinical efficacy and feasibility of whey protein isolates supplementation in malnourished peritoneal dialysis patients: A multicenter, parallel, open-label randomized controlled trial

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ARTICLE INFO

Article history:
Received 29 March 2018
Accepted 2 April 2018

Keywords:
Whey protein
Protein supplementation
Peritoneal dialysis
Malnutrition
Nutritional status

SUMMARY

Background and aims: Poor dietary intake is commonly associated with malnutrition in the dialysis population and oral nutritional supplementation is strategized to redress dietary inadequacy. Knowledge on clinical efficacy of whey protein supplementation (WPS) as an option to treat malnutrition in continuous ambulatory peritoneal dialysis (CAPD) patients is limited.

Methods: This multicenter, parallel, open-label, randomized controlled trial investigated the clinical efficacy of WPS in 126 malnourished CAPD patients with serum albumin <40 g/L and body mass index (BMI) <24 kg/m^2. Patients randomized to the intervention group (IG, n = 65) received protein powder (27.4 g) for 6 months plus dietary counseling (DC) while the control group (CG, n = 61) received DC only. Anthropometry, biochemistry, malnutrition-inflammation-score (MIS), dietary intake inclusive of dialysate calories, handgrip strength (HGS) and quality of life (QOL) were assessed at baseline and 6 months. Clinical outcomes were assessed by effect size (Cohen's *d*) comparisons within and between groups.

Results: Seventy-four patients (n = 37 per group) completed the study. Significantly more IG patients (59.5%) achieved dietary protein intake (DPI) adequacy of 1.2 g/kg per ideal body weight ($p < 0.001$) compared to CG (16.2%) although difference in the adequacy of dietary energy intake between groups was non-significant ($p > 0.05$). A higher DPI paralleled significant increases in serum urea (mean Δ: IG = +2.39 ± 4.36 mmol/L, $p = 0.002$, $d = 0.57$ *vs* CG = −0.39 ± 4.59 mmol/L, $p > 0.05$, $d = 0.07$) and normalized protein catabolic rate, *n*PCR (mean Δ: IG = +0.11 ± 0.14 g/kg/day, $p < 0.001$, $d = 0.63$ *vs* CG = +0.001 ± 0.17 g/kg/day, $p > 0.05$, $d = 0.09$) for IG compared to CG patients. Although not significant, comparison for changes in post-dialysis weight (mean Δ: +0.64 ± 1.16 kg *vs* +0.02 ± 1.36 kg, $p = 0.076$, $d = 0.58$) and mid-arm circumference (mean Δ: +0.29 ± 0.93 cm *vs* −0.12 ± 0.71 cm, $p = 0.079$, $d = 0.24$) indicated trends favoring IG *vs* CG. Other parameters remained unaffected by treatment comparisons. CG patients had a significant decline in QOL physical component (mean Δ = −6.62 ± 16.63, $p = 0.020$, $d = 0.47$). Using changes in *n*PCR level as a marker of WPS intake within IG, 'positive responders' achieved significant improvement in weight, BMI, skinfold measures and serum urea (all $p < 0.05$), while such changes within 'negative responders' were non-significant (all $p > 0.05$).

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https://doi.org/10.1016/j.clnesp.2018.04.002

Conclusion: A single macronutrient approach with WPS in malnourished CAPD patients was shown to achieve DPI adequacy and improvements in weight, BMI, skin fold measures, serum urea and *n*PCR level. *Clinical trial registry:* www.clinicaltrials.gov (NCT03367000).

Abbreviations

BMI	Body mass index
CAPD	Continuous ambulatory peritoneal dialysis
CG	Control group
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DC	Dietary counseling
DEI	Dietary energy intake
DPI	Dietary protein intake
FTM	Fat tissue mass
GLM	General linear model
HD	Hemodialysis
HGS	Hand grip strength
hsCRP	high-sensitivity C-reactive protein
IBW	Ideal body weight
IG	Intervention group
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	Dialysis adequacy
LTM	Lean tissue mass
MAC	Mid-arm circumference
MAMA	Mid-arm muscle area
MAMC	Mid-arm muscle circumference
MCS	Mental component score
MIS	Malnutrition inflammation score
NMRR	National Medical Research Registry
*n*PCR	Normalized protein catabolic rate
NR	Negative responder
ns	Not significant
PCS	Physical component score
PD	Peritoneal dialysis
PR	Positive responder
QOL	Quality of Life
SF36	36-item Short Form Health Survey
TSF	Triceps skinfold
WPS	Whey protein supplementation

1. Introduction

Malnutrition in chronic kidney disease (CKD) patients undergoing peritoneal dialysis (PD) is a common issue with global incidence ranging from 18 to 56% [1]. In Malaysia, where continuous ambulatory peritoneal dialysis (CAPD) is the mainstay PD therapy for 3619 patients, about 60% are considered malnourished [2]. Poor dietary intake is an acknowledged major cause of malnutrition in dialysis patients, for both PD and hemodialysis (HD) patients [3,4], as achieving actual energy and protein sufficiency are major challenges [5,6]. The underlying mechanism of uremic metabolism in CKD affects appetite, while the presence of anorexia and inflammation exacerbates poor food intake [7]. Additionally, the intra-abdominal pressure from PD fluids induces a sense of abdominal fullness leading to poor dietary intake [8].

PD patients have greater requirement for protein intake (1.2–1.3 g/kg body weight) as they have high daily dialysate losses of proteins amounting to 6–8 g per day [4,9,10] as well as face greater risk for uremia-induced protein degradation [11]. The likely negative nitrogen balance in this population is further compromised with food aversion towards protein foods [12]. Thus, dietary protein deficits in PD patients pose an increased challenge to achieving nutrition repletion [9,10,13].

Provision of protein supplementation to achieve repletion appears to be a priority in malnourished PD patients with a background of poor oral intake as they receive adjuvant dialysate calories up to 400 kcal per day depending on the concentration and volume of the dextrose-enriched dialysate exchange fluids [13]. Tennankore and Bargman (2013) highlighted a potential risk of excess caloric intake in PD patients with high glucose absorption from the dialysate leading to obesity and morbidity [14]. We therefore hypothesized that as PD patients receive additional calories through the 4-times per day dialysate exchanges, achieving dietary protein intake (DPI) adequacy through protein supplementation should be the priority to address malnutrition. To date, 12 studies [4,5,10,15–23] have examined oral protein supplementation for PD patients without malnutrition. Until now, the benefits of protein supplementation in malnourished PD patients with or without protein energy wasting are not clearly established. Generally, lower normalized protein catabolic rate (*n*PCR) levels are associated with presence of malnutrition [10,24]. Taking these issues into account, our study specifically recruited malnourished CAPD patients to receive whey protein supplementation (WPS) and included *n*PCR as a measure to reflect compliance towards supplementation. The choice of whey protein for supplementation in this study was because of its high biological value and content of branched chain amino acids, which support muscle recovery through greater stimulation of protein uptake and synthesis [17].

2. Materials and methods

2.1. Study design and patient recruitments

This multicenter, parallel, open-label, randomized controlled trial was conducted over a period of 18 months from February 2012 to August 2013 in CAPD units of 3 tertiary hospitals in Malaysia. The study was approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (NMRR-11-355-9148) and Medical Research Ethics Committee of National University of Malaysia (FF-274-2012) and was also registered on www.clinicaltrials.gov (NCT03367000).

Sample size was calculated using *n*PCR as a primary outcome, with a power of 80% (effect size of 0.5143), which yielded a

minimum of 46 patients per arm to achieve significance. Assuming a 20% dropout, the final recruitment was set as 56 patients per arm.

A total of 185 patients from the study sites consented to be screened for the study. Of these, 140 patients became eligible based on the inclusion criteria of [i] dialyzing for ≥6 months [ii] aged ≥18 years and [iii] presence of malnutrition using the Kidney Disease Outcomes Quality Initiative (KDOQI) criteria of serum albumin <40 g/L and body mass index (BMI) < 24 kg/m^2 [9]. Patients with repeated history of hospitalization or inter-current illnesses in the past six months prior to the recruitment or diagnosed with high inflammatory diseases or malignancy were excluded.

2.2. Treatment groups

Consenting patients were randomized (in 1:1 ratio based on the number of subjects recruited at each centre) to either the intervention group (IG) or the control group (CG) using a computerized randomizing calculator after baseline data was collected. Randomization was performed by the study statistician [KC] who was not clinically involved in the trial. Treatment was provided for 6 months with the IG receiving WPS and dietary counseling (DC) whilst CG received only DC. Two 15 g WPS sachets were to be consumed daily by IG patients which added 27.4 g protein and 116 kcal to their daily nutritional intake. The WPS was in powder form containing 90–94% whey protein isolate and hydrolyzed whey enabling a complete amino acid composition (Ceprolac, Aspen Sarl Sdn Bhd). The protein powder was required to be dissolved in 75–100 ml of water at room temperature and ingested post-meal once daily. The nutritional composition of the supplement is provided as a Supplementary file 1. Patients in both groups received standard DC provided by a dietitian, which was to optimize dietary calorie and protein intake as per KDOQI guidelines with follow up at baseline, 3rd month and 6th months of the study.

2.3. Compliance and acceptability

Compliance and acceptability of the supplement including gastrointestinal tolerance were monitored via phone call and monthly home visits. Patients recorded their daily intake of the supplement and these records were submitted monthly. Counts of returned empty sachets of supplements also served to measure compliance. Acceptability of the supplement was recorded by IG patients monthly using a 5-point Likert-scale (*strongly agree, agree, neutral, disagree, strongly disagree*), indicating taste, flavor, portion, odor and early satiety.

2.4. Outcome measurements

Evaluations included anthropometric measurements, body composition, laboratory assessment, nutritional status assessment, dietary and appetite assessment, quality of life (QOL), and hand grip strength (HGS) testing. Trial procedures were carried out at baseline and end of the 6th month of study for all parameters.

[i] Anthropometry - Anthropometric measurements were performed by a single dietitian to eliminate inter-observer

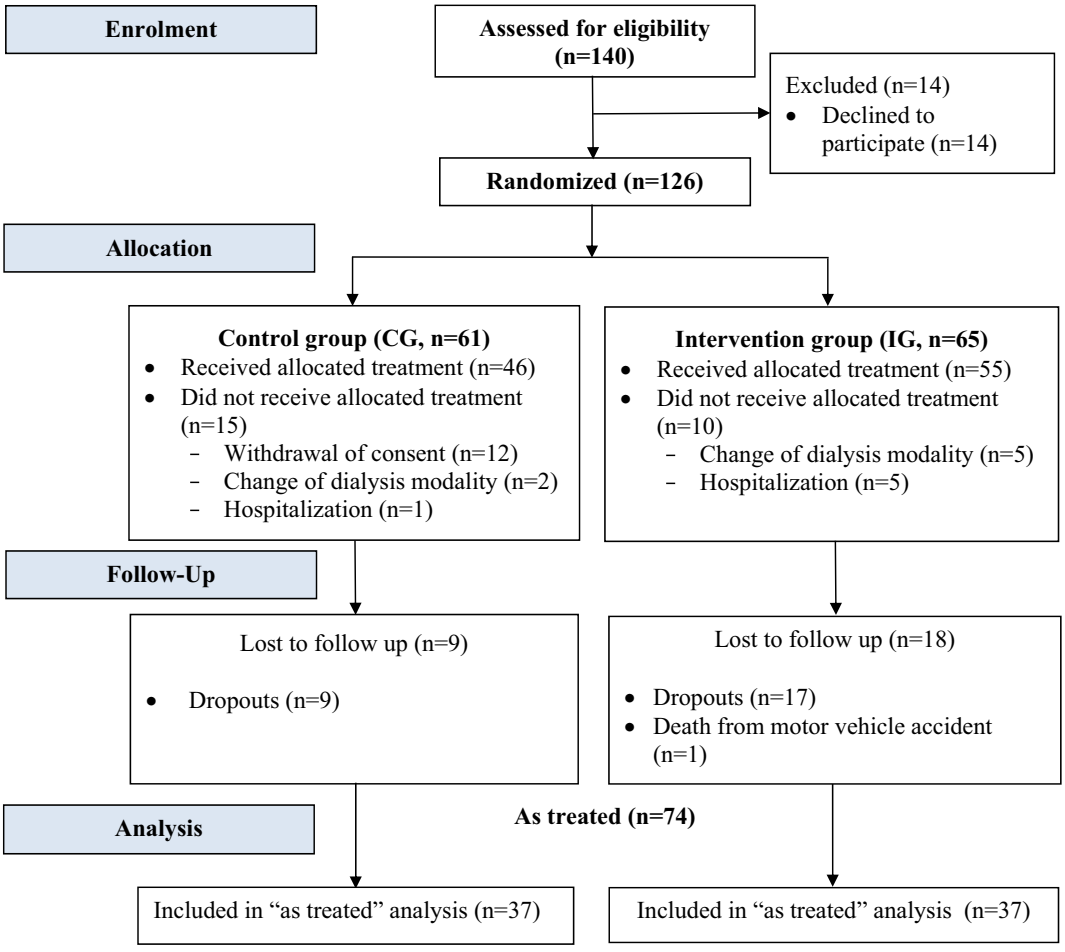

Fig. 1. Study flow of participants.

variation. These included post-dialysis weight (SECA, Model 220, SECA, Germany), which together with height was used to derive BMI. Measurements for triceps skinfold thickness (TSF) were performed as per International Society for the Advancement of Kinanthropometry [25] protocol on the dominant or non-fistula arm with a Harpenden skinfold caliper (HSK-BI, British Indicators, West Sussex, UK), and mid-upper arm circumference (MAC) with a non-stretchable Lufkin® tape (Apex Tool Group, LLC, NC, USA). The mid-arm muscle circumference (MAMC) and mid-arm muscle area (MAMA) were calculated using the following equations [26]:

$$MAMC\ (\text{cm}) = MAC\ (\text{cm}) - [TSF\ (\text{cm}) \times \pi]$$

$$MAMA\ \left(\text{cm}^2\right) = MAMC\ (\text{cm})^2 \Big/ 4\pi - 10.0\ (\textit{for men})\ \textit{or}\ 6.5\ (\textit{for women})$$

[ii] Body composition - Body composition was assessed using a portable whole-body bio-impedance spectroscopy device (Body Composition Monitor, Fresenius Medical Care, Bad Homburg, Germany) with the patient resting in the supine position. The hydration status, lean tissue mass (LTM) and fat tissue mass (FTM) generated by the instrument were based on a physiologic tissue model as described by Chamney et al. (2007) [27].

[iii] Laboratory investigations - Using automated clinical chemistry (Roche/Hitachi 912 System, Roche Diagnostics, Tokyo, Japan), measurements were performed covering serum urea by urease-glutamate dehydrogenase method, creatinine by Jaffe method, total iron-binding capacity by precipitation method with magnesium hydroxide carbonate, albumin by bromocresol green method, total protein by colorimetric method. Additionally, serum high-sensitivity C-reactive protein (hsCRP) was measured by immunoturbidimetric assay. Analyses were carried out as per in-house standard operating procedures accredited by the Ministry of Health, Malaysia. Dialysis adequacy (Kt/v) and *n*PCR were determined based on the urea kinetic modeling [28].

[iv] Dietary and appetite assessment - The 24-h dietary records were collected for 3 days, inclusive of 2 random weekdays and one optional weekend day, in order to determine mean nutritional intake [3]. These records were analyzed for energy and protein intake using the Nutritionist Pro™ 2.2.16 software (First DataBank Inc., 2004), which includes a database for ethnic-specific Malaysian foods [29,30]. Appetite assessment was also performed using a previously validated tool for the Malaysian dialysis population [31,32].

[v] Nutritional status assessment - The Malnutrition Inflammation Score (MIS) rating was performed to assess the severity of malnutrition-inflammation complex syndrome on nutritional status [33,34]. It combines the traditional 7 components of subjective global assessment with BMI, serum albumin and total iron binding capacity. The cumulative score for MIS ranges between 0 (*normal*) to 30 (*severely malnourished*).

[vi] QoL assessment - QoL was assessed using an interviewer-administered 36-item Short Form Health Survey (SF-36) questionnaire [35]. The total of two domains in SF-36, namely the physical component scale (PCS) for assessing physical health status and the mental component scale (MCS) for assessing emotional function contributed to the total QoL score [36].

[vii] HGS test - HGS test, as a surrogate measure of muscle strength [37] was carried out using the Jamar dynamometer (BK-7498; Fred Sammons, Inc., Burr Ridge, IL) on the dominant or non-fistula hand. Three readings were taken and the median value was used.

3. Statistical analysis

An "as treated' analysis was adopted which excluded dropouts and patients with compliance <50%. Dietary energy intake (DEI) and DPI were interpreted in terms of patients' ideal body weight (IBW). Outcomes were presented as frequency (percentages) or mean ± standard deviation. The normal distribution of continuous variables was assessed using Kolmogorov–Smirnov test. Since age was significantly different between groups at baseline, this was factored in for subsequent analysis as a covariance. Differences within groups were analyzed using one-way repeated measures ANOVA for normally distributed continuous data. Differences between groups for mean change were analyzed using the general linear model (GLM) test. The Student's *t*-test was used to investigate the differences in mean change between groups in the same evaluation. Categorical variables were evaluated for differences using chi-square test. In addition, patients were categorized into 'positive' or 'negative responders' according to change in *n*PCR levels post-treatment. Nutritional outcomes for this sub-analysis were assessed using one-way repeated measures ANOVA for differences within groups and GLM test for differences between groups. All analyses were computed using the IBM Statistical Package for Social Sciences version 23.0 (IBM SPSS Statistics Inc. Chicago IL. USA) with significance set at $p < 0.05$ for all parameters. Effect sizes were computed using Cohen's *d* to compare magnitude of changes for interventional outcomes and interpreted as negligible (<0.2), moderate (~0.5) or large (>0.8) [38].

4. Results

Among the 140 eligible patients, 126 consented for the study and were randomly assigned to either CG (n = 61) or IG (n = 65). Twenty-five subjects did not receive the allocated treatment due to change of dialysis modality (n = 7), early withdrawal of consent (n = 12) and hospitalization prior to treatment (n = 6). Seventy-four

Table 1
Baseline characteristic of patients.

Patient characteristics[a,b]	Intervention Group (IG, n = 37)	Control Group (CG, n = 37)	*p*-value[c]
Age (years)	50.84 ± 15.20	42.14 ± 14.57	0.014
Dialysis vintage (years)	3.27 ± 3.03	3.19 ± 2.59	ns
Dialysate calories (kcal)	260 ± 59	274 ± 63	ns
Hydration status			
Normal	18 (48.6%)	20 (54.1%)	ns
Over-hydration	19 (51.4%)	17 (45.9%)	
Gender			
Male	17 (45.9)	15 (40.5)	ns
Female	20 (54.1)	22 (59.5)	
Ethnicity			
Malay	25 (67.6)	22 (59.5)	ns
Chinese	8 (21.6)	12 (35.1)	
Indian	4 (10.8)	2 (5.4)	
Education level			
Primary	7 (18.9)	9 (24.3)	ns
Secondary	19 (51.4)	15 (40.5)	
Tertiary	11 (29.7)	13 (35.1)	
Income level			
<RM1000	21 (56.8)	20 (54.1)	ns
>RM1000	16 (43.2)	27 (45.9)	
Co-morbidities			
Hypertension	30 (81.1)	28 (75.7)	ns
Diabetes	11 (29.7)	8 (21.6)	ns
CVD	4 (10.8)	4 (10.8)	ns

Abbreviations: CVD = Cardiovascular disease; ns = not significant.
[a] Data expressed as mean ± standard deviation for continuous data; n (%) for categorical data.
[b] Frequency data was analyzed using chi-square test whilst continuous data was analyzed using Student's t-test.
[c] All *p*-values <0.05 were indicative of significance.

subjects completed the 6-month treatment period with 37 patients each in both groups (Fig. 1).

There was no difference ($p > 0.05$) between groups at baseline for dialysis vintage, dialysate calories, hydration status, gender, ethnicity, education and income level and co-morbidities except for age ($p = 0.014$) (Table 1).

Within and between group comparisons for outcomes are provided in Table 2.

4.1. Nutritional outcomes

IG compared to CG experienced significant moderate increases in serum urea (mean Δ: +2.39 ± 4.36 mmol/L *vs* −0.39 ± 0.59 mmol/L, $p = 0.003$, $d = 0.53$), large increases in *n*PCR (mean Δ: +0.11 ± 0.14 g/kg/day *vs* +0.001 ± 0.17 g/kg/day, $p = 0.022$, $d = 0.80$) and protein intake (mean Δ: +23.19 ± 13.34 g *vs* +2.28 ± 15.27 g, $p < 0.001$, $d = 1.60$). Comparatively, changes in post-dialysis weight (mean Δ: +0.64 ± 1.16 kg *vs* +0.02 ± 1.36 kg, $p = 0.076$, $d = 0.58$) and MAC (mean Δ: +0.29 ± 0.93 cm *vs* −0.12 ± 0.71 cm, $p = 0.079$, $d = 0.24$), although not significant, showed trends favoring IG *vs* CG. Other parameters remained unaffected by treatment comparisons.

4.2. Body composition

At the end of 6 months of treatment, reductions in LTM (mean Δ = −0.87 ± 2.49 kg, $p = 0.041$, $d = 0.13$) but gain in FTM (mean

Table 2
Comparison of nutritional measures between the intervention (IG) and control group (CG)[a].

Outcomes	Timeline	IG (n = 37)	Mean Δ ± SD	*p*-trend ^{IG} (*d*)	CG (n = 37)	Mean Δ ± SD	*p*-trend ^{CG} (*d*)	*p*-trend $^{IG\ vs\ CG}$ (*d*)
Post-dialysis weight (kg)	S_0	54.21 ± 8.41	0.64 ± 1.16	0.002	52.63 ± 8.61	0.02 ± 1.36	0.914	0.076
	S_6	54.85 ± 8.93		(0.07)	52.65 ± 8.37		(0.00)	(0.58)
BMI (kg/m^2)	S_0	21.65 ± 2.81	0.25 ± 0.45	0.002	21.22 ± 2.35	0.03 ± 0.55	0.755	0.103
	S_6	21.91 ± 3.01		(0.09)	21.25 ± 2.37		(0.01)	(0.52)
MAC (cm)	S_0	26.28 ± 3.05	0.29 ± 0.93	0.062	25.28 ± 2.94	−0.12 ± 0.71	0.319	0.079
	S_6	26.58 ± 3.17		(0.10)	25.16 ± 3.05		(0.04)	(0.24)
TSF (mm)	S_0	13.33 ± 6.44	0.13 ± 1.29	0.540	12.34 ± 6.00	−0.11 ± 1.19	0.589	0.328
	S_6	13.46 ± 6.05		(0.04)	12.23 ± 6.02		(0.02)	(0.02)
MAMC (cm^2)	S_0	22.10 ± 2.43	0.25 ± 0.93	0.110	21.40 ± 2.41	−0.08 ± 0.79	0.520	0.209
	S_6	22.35 ± 2.57		(0.10)	21.32 ± 2.60		(0.03)	(0.23)
MAMA (cm^2)	S_0	31.20 ± 8.06	0.97 ± 3.26	0.079	28.89 ± 7.73	−0.15 ± 2.83	0.747	0.261
	S_6	32.17 ± 8.58		(0.12)	28.74 ± 8.40		(0.02)	(0.32)
LTM (kg)	S_0	32.39 ± 6.74	−0.87 ± 2.49	0.041	32.66 ± 6.72	−0.003 ± 0.52	0.975	0.107
	S_6	31.52 ± 6.70		(0.13)	32.66 ± 6.74		(0.00)	(0.57)
FTM (kg)	S_0	14.85 ± 5.97	1.03 ± 2.82	0.033	13.28 ± 4.89	0.10 ± 3.94	0.875	0.487
	S_6	15.88 ± 6.33		(0.17)	13.38 ± 5.70		(0.02)	(0.32)
Serum urea (mmol/L)	S_0	13.54 ± 3.93[b]	2.39 ± 4.36	0.002	17.80 ± 5.55[b]	−0.39 ± 4.59	0.612	0.003
	S_6	15.93 ± 4.45		(0.57)	17.41 ± 5.35		(0.07)	(0.53)
Serum creatinine (μmol/L)	S_0	811 ± 310[b]	−6.32 ± 204.32	0.852	982 ± 328[b]	15.81 ± 161.72	0.584	0.327
	S_6	805 ± 276[b]		(0.02)	997 ± 293[b]		(0.05)	(0.06)
Serum albumin (g/L)	S_0	33.65 ± 3.82	1.35 ± 4.69	0.088	32.36 ± 4.28	3.42 ± 4.31	<0.001	0.174
	S_6	35.00 ± 4.50		(0.32)	35.78 ± 5.28		(0.72)	(0.54)
Total protein (g/L)	S_0	69.76 ± 6.08	3.59 ± 6.60	0.002	69.08 ± 6.12	3.03 ± 6.69	0.010	0.425
	S_6	73.35 ± 6.62		(0.57)	72.11 ± 7.68		(0.44)	(0.10)
Serum phosphate (mmo/L)	S_0	1.53 ± 0.44	−0.02 ± 0.34	0.664	1.55 ± 0.53	0.09 ± 0.42	0.203	0.211
	S_6	1.51 ± 0.43		(0.05)	1.64 ± 0.59		(0.16)	(0.22)
Kt/v	S_0	2.26 ± 0.52	−0.04 ± 0.30	0.436	2.28 ± 0.61	−0.06 ± 0.33	0.271	0.700
	S_6	2.22 ± 0.50		(0.08)	2.22 ± 0.66		(0.09)	(0.08)
*n*PCR (g/kg/day)	S_0	0.83 ± 0.19[b]	0.11 ± 0.14	<0.001	1.03 ± 0.26[b]	0.001 ± 0.17	0.613	0.022
	S_6	0.94 ± 0.16		(0.63)	1.01 ± 0.21		(0.09)	(0.80)
hsCRP (mg/dL)	S_0	2.90 ± 4.10	2.35 ± 7.70	0.071	3.32 ± 6.68	2.72 ± 16.26	0.329	0.872
	S_6	5.25 ± 8.71		(0.37)	6.04 ± 14.91		(0.35)	(0.03)
MIS score	S_0	7.66 ± 2.89	0.09 ± 1.93	0.794	8.11 ± 3.28	0.17 ± 2.36	0.670	0.956
	S_6	7.74 ± 2.57		(0.03)	8.29 ± 3.44		(0.05)	(0.04)
PCS	S_0	73.16 ± 13.59	−2.56 ± 14.04	0.275	75.20 ± 10.57	−6.62 ± 16.53	0.020	0.397
	S_6	70.61 ± 16.35		(0.17)	68.58 ± 17.54		(0.47)	(0.31)
MCS	S_0	73.09 ± 13.69	3.22 ± 13.45	0.154	76.04 ± 12.59	−1.33 ± 13.62	0.557	0.299
	S_6	76.31 ± 11.96		(0.25)	74.71 ± 13.59		(0.10)	(0.16)
SF-36	S_0	76.01 ± 12.52	0.46 ± 12.96	0.831	79.31 ± 10.13	−4.89 ± 14.46	0.047	0.206
	S_6	76.47 ± 13.60		(0.04)	74.42 ± 15.55		(0.38)	(0.38)
HGS (kg)	S_0	18.92 ± 8.47	−0.22 ± 4.47	0.770	18.11 ± 7.79	−1.24 ± 3.72	0.050	0.288
	S_6	18.70 ± 7.49		(0.03)	16.86 ± 7.33		(0.17)	(0.29)
Energy (kcal)[c]	S_0	1401 ± 197	30.78 ± 138.74	0.186	1438 ± 319	54.49 ± 156.85	0.042	0.767
	S_6	1432 ± 237		(0.14)	1492 ± 318		(0.17)	(0.18)
Protein (g)	S_0	42.83 ± 11.52	23.19 ± 13.34	<0.001	46.36 ± 11.50	2.28 ± 15.27	0.371	<0.001
	S_6	66.01 ± 13.31[b]		(1.87)	48.64 ± 14.53[b]		(0.18)	(1.60)

Abbreviations: BMI = Body Mass Index; FTM = fat tissue mass; HGS = hand grip strength; hsCRP = high-sensitivity C-reactive protein; Kt/V = dialysis adequacy; LTM = lean tissue mass; MAC = mid-arm circumference; MAMA = mid-arm muscle area; MAMC = mid-arm muscle circumference; MIS = Malnutrition Inflammation Score; *n*PCR = normalized protein catabolic rate; SF-36 = short-form (36-item) questionnaire; SF-36 MCS = SF-36 mental health score; SF-36 PCS = SF-36 physical health score; TSF = triceps skinfold; S_0 = Study baseline; S_6 = End of 6 months of study.
*Significance for $p < 0.05$.
[a] Data adjusted for age, Cohen's *d* effect size: negligible (<0.2), moderate (~0.5) or large (>0.8).
[b] Same superscript indicate data was significantly different in the same evaluation.
[c] Energy intake inclusive of dialysate calorie.

$\Delta = +1.03 \pm 2.82$ kg, $p = 0.033$, $d = 0.17$) occurred within IG, whereas no change occurred within CG for either parameter (both $p > 0.05$). Between group comparisons were not significant for both LTM and FTM ($p > 0.05$).

4.3. Inflammation marker (hsCRP)

Differences within and between groups were not significant ($p > 0.05$).

4.4. Dietary adequacy

Dietary assessment at end of study indicated calorie deficits <30 kcal/kg IBW for both IG (81.1%) and CG (75.7%) patients, despite deriving 281 ± 64 kcal from daily dialysate exchanges. As expected IG patients had significantly fewer patients (40.5%, $p < 0.001$) with protein intake <1.2 g/kg/day IBW compared to CG (83.8%).

4.5. MIS and appetite scores

Based on MIS categorization, more IG patients (15/37, 42.9%) compared to CG patients (11/37, 29.7%) showed improvement in their nutritional status. Less IG patients (9/37) than CG patients (15/37) reported improvement in appetite (Fig. 2). Neither MIS nor appetite scores were significantly different for categorical comparisons between groups ($p > 0.05$).

4.6. QoL

There was no change in QoL components within IG. Within CG, a moderately significant decreases in SF-36 physical component score (mean $\Delta = -6.62 \pm 16.53$, $p = 0.020$, $d = 0.47$) and a small change in SF-36 total score (mean $\Delta = -4.89 \pm 14.46$, $p = 0.047$, $d = 0.38$) occurred. QoL components were not significantly different ($p > 0.05$) between groups.

4.7. Physical strength (HGS)

The between group difference for HGS was not significant ($p > 0.05$).

4.8. nPCR as a measure of dietary protein compliancy

All patients were categorized according to improvement in *n*PCR levels over the 6 months, which yielded overall 34 'positive responders' (IG = 26 *vs* CG = 18), 23 'negative responders' (IG = 7 *vs* CG = 16) and 17 'neutral responders' (no change in *n*PCR levels). The subsequent analysis only compared 'positive and negative responders' (Fig. 3). Mean DPI for these groups were IG positive responders = 66.46 ± 13.35 g, IG negative responders = 59.26 ± 11.41 g, CG positive responders = 46.71 ± 10.23 g and CG negative responders = 52.73 ± 17.91 g respectively. IG positive responders (Δ *n*PCR level = 0.16 ± 0.11 g/kg/day) achieved significant improvements in MAC ($p = 0.006$), MAMC ($p = 0.031$) and MAMA ($p = 0.033$) compared to the CG positive responders (Δ *n*PCR level = 0.12 ± 0.12 g/kg/day). Compared to baseline, IG positive responders showed significant improvement in weight ($p = 0.014$), BMI ($p = 0.015$), MAC ($p = 0.006$), MAMC ($p = 0.023$) and MAMA ($p = 0.022$). These effects were not observed either within the IG negative responders or the CG group. Larger declines (~5–10%) in HGS, although not significant ($p > 0.05$), occurred in all groups except in the IG positive responders (<0.5%). IG positive responders also demonstrated significant increases in serum urea ($p = 0.002$), which were not observed in the other groups. More 'positive responders' were observed in IG compared CG for MIS scoring indicating improvement in nutritional status (IG PR = 60% *vs* CG PR = 50%). But in terms of appetite, both IG and CG reported similar rates of appetite improvement (PR = 89% for both IG and CG, $p > 0.05$).

4.9. Product tolerance

General compliance towards the product was perceived as good with an overall 75 ± 18% WPS intake maintained over 6 months. Patient scoring for taste (92%, n = 34), flavor, (89%, n = 33) and

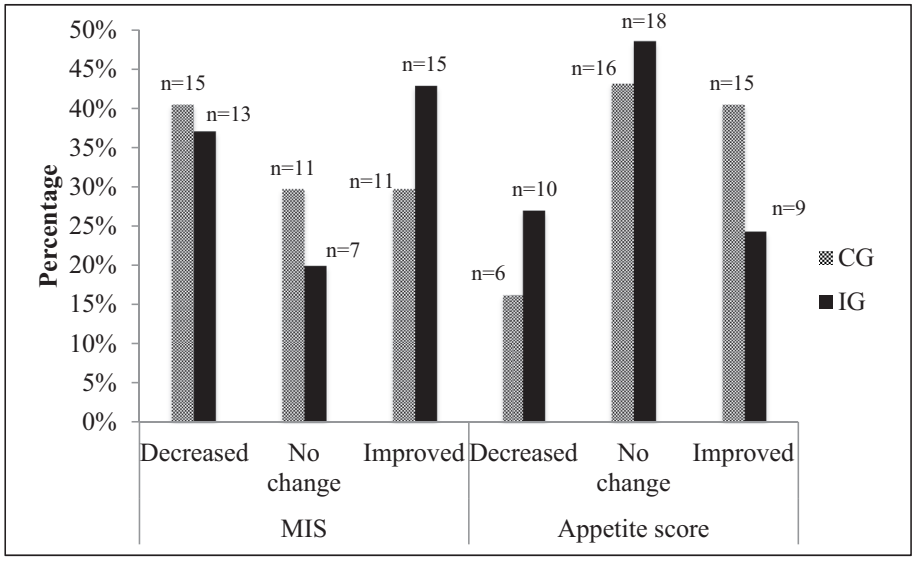

Fig. 2. Categorical changes in MIS and appetite scores between treatment groups. Abbreviations: CG = control group; IG = intervention group; MIS = Malnutrition-inflammation score.

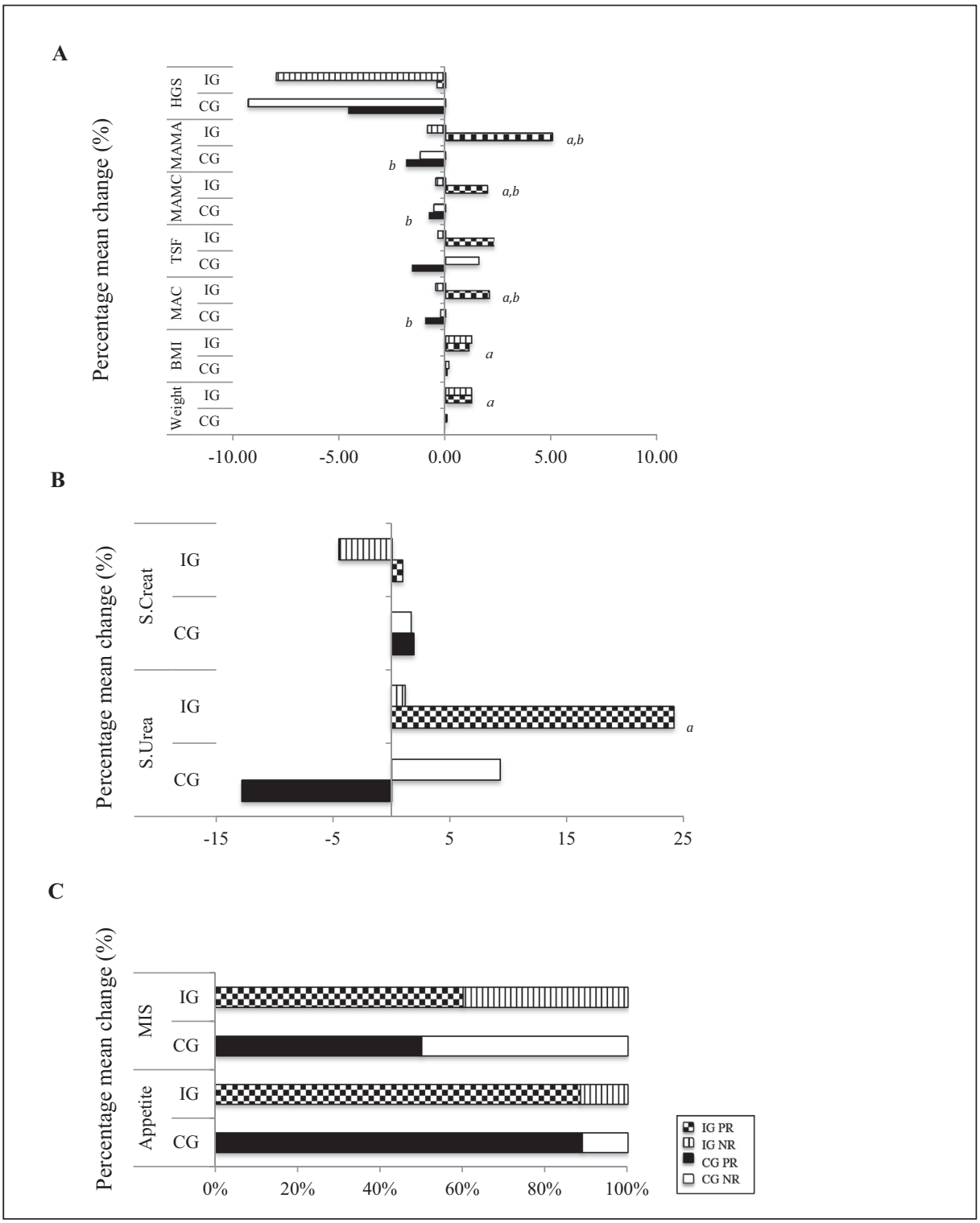

Fig. 3. Improvement in nutritional parameters as per *n*PCR categorization. **A**-Anthropometry and physical measures; **B**-Biochemical parameters and **C**- MIS and appetite scores. Abbreviations: BMI = Body mass index; CG = control group; HGS = Hand grip strength; IG = intervention group; MAC = mid-arm circumference, MAMA = mid arm muscle area; MAMC = mid-arm muscle circumference; MIS = malnutrition-inflammation score; NR = negative responder; PR = positive responder; S. Creat = serum creatinine; S.Urea = serum urea; TSF = triceps skin fold. [a] Significant difference within IG PR ($p < 0.05$). [b] Significant difference between IG PR & CG PR ($p < 0.05$), data adjusted for age.

portion size without affecting satiety (89%, n = 33) indicated good acceptance for the product. However, some patients gave negative scores for odor (27%, n = 10). Minor complaints associated with WPS were skin itchiness (n = 1), muscle ache (n = 1), nausea (n = 2) and lack of appetite (n = 2). Only one IG patient was observed to have increased serum potassium and phosphate levels attributed to reported intake of nutrient-rich dietary foods rather than WPS.

5. Discussion

Current knowledge on oral nutrition supplementation to address the likely negative nitrogen balance in malnourished PD patients is limited. Studies are few and inconclusive in terms of nutritional status improvement, and varying in interpretation because of issues of treatment period, poor compliance, product tolerance and patient dropout rates [5,10,17,22]. Co-existence of multiple co-morbidities, hospitalization and infection in PD patients also modulate poorer response to nutrition supplementation [20].

The choice of oral whey protein isolates relates to its better substrate utilization for muscle recovery [17] and low phosphorous content which is desirable when planning high protein diets, given risks for hyperphosphatemia and renal osteodystrophy in CKD patients [39]. A single-nutrient approach with modular protein is an important hypothesis to test as theoretically dialysate dextrose calories supplement dietary calories for PD patients, whereas achieving DPI adequacy would be the major nutritional priority. Past options have examined commercial formulas [21], calcium casein [15] or egg albumin [5,17] powder. Jeloka et al. (2013) who unsuccessfully supplemented 50 PD patients with whey protein or egg albumin, had issues with poor compliance (<50% intake) and high dropout rate (32%) [19]. Contrarily, Hassan (2017) reported significant increases in serum albumin and *n*PCR levels after 12 weeks of whey protein supplementation in 18 PD patients, but interpretations were limited by small sample size, high dropout rate, lack of dietary intake data and a single-center design.

Anthropometric changes as per post-dialysis weight, MAC, TSF, MAMC and MAMA were not substantial enough ($d < 0.2$) to allow deductions on the benefits of supplementation given the short period of the trial as well as frequent contact with the dietitian. Increased serum albumin levels were observed within both IG (+1.35 g/L, $d = 0.32$) and CG (+3.42 g/L, $d = 0.72$) patients post-intervention which is again the likely effect of patient contact with the dietitian. Based on previous studies, depending on serum albumin for measuring intervention outcome is inadequate [4,5,10,15–19,21–23,40,41] as findings may be confounded by hydration and inflammation status [4,40,42]. However, between group comparisons were significant for serum urea (moderate), *n*PCR (large), and DPI (large) for the supplemented compared to control patients.

IG patients had increased FTM along with decreased LTM similarly observed in HD patients [43]. Some studies note LTM, an indicator for muscle mass, has a greater protective role against mortality rather than FTM [44,45]. Marcelli et al. (2015) reported HD patients with higher fat tissue index and lower lean tissue index had a better survival rate [43]. Delgado et al. (2017) observed percent body fat, a proxy of subcutaneous fat, was not associated with CRP and inversely associated with IL-6 in HD patients [46], whereas in a PD population [47] increases in fat tissue index was associated with inflammation. An increase in fat mass over time may reflect positive change as a physiological priority to spare muscle tissue as a likely scenario in patients with muscle wasting.

Given issues affecting supplementations targeting PD patients [5,15,17,19,21,40,41], we elected to report outcomes based on not just cause-effect relationships but also whether greater compliancy (based on increased nPCR) translated into improved nutritional outcomes in *post hoc* analyses [48]. Compliance to protein supplementation yielded sizeably large nPCR ($d = 0.80$) and moderate serum urea ($d = 0.53$) increases in IG patients, which are expected outcomes [9,15] and signify nPCR as a marker of nutrition status [10] while urea production also signifies metabolic breakdown of exogenous protein [15]. In agreement with Moretti et al. (2009) [10], we observed *n*PCR increases for IG patients did not correlate with serum albumin unlike another study [9]. In *post hoc* analysis based on increased *n*PCR levels compared to baseline, IG 'positive responders' versus CG 'positive responders' experienced significant improvements in nutritional status. This observation strengthens the view that supplementation-induced anthropometric changes are possible, and a positive indicator of improvement of both muscle and fat stores only in patients with good compliance [22]. Improvements observed in IG 'positive responders' (n = 27) can be attributed to true compliance towards supplementation, despite the overall acceptable compliance rate of 75% for the supplemented group [42].

Although we aimed for a single-nutrient approach to address protein-repletion, we found that our patients actually received 281 kcal from the glucose-based PD solutions, indicating an overall suboptimal energy intake was a co-issue. Additionally, some IG patients reporting early satiety, opted to miss meals when taking WPS leading to suboptimal energy intakes despite a 23% increased protein intake from baseline. Indeed, a higher energy (+116 kcal)-lower protein (−7 g) consumption pattern in negative responders emerged *as the difference with positive responders,* although non-significant. Early satiety is associated with high protein diets as elevated blood amino acid levels suppress the appetite hormone, leptin, with accompanying low energy intakes and weight loss [49]. Admittedly overall DEI was suboptimal for both groups, and this requires attention as gluconeogenesis promotes diversion of protein substrates to fuel energy supply in condition of suboptimal dietary intake [11].

Serum phosphate levels were unaffected in IG patients, which is desirable for CKD patients. Indeed, whey proteins have a phosphorus-to-protein ratio <1 mg/g compared to egg albumin (<5 mg/g), whole egg (<15 mg/g) and animal proteins (7–29 mg/g) [39,50]. Additionally, CG patients showed significant decline in QOL scores while IG patients remained unchanged. Feeling of trust in patients during treatment with a beneficial product may have prevented any further decline in their QOL [51].

Our multi-centered study with standardized data collection protocols provided scoping evidence in understanding the effectiveness of WPS in malnourished PD patients. These patients did not report any issues related to compliance with WPS. The PD patient group is known to have poor compliance towards nutrition supplementation and we purposely evaluated nutritional outcomes targeting compliance. Although the study period was 6 months, a longer duration of feeding may be necessary towards achieving nutritional efficacy signified by substantially improved body weight status. A high dropout rate of 41% was a limitation to this study but was unrelated to poor compliance.

In conclusion, a 6-month WPS feeding improved markers of nutritional status in malnourished CAPD patients with good compliance and tolerance to the product. The study provides evidence supporting the beneficial approach of the single-nutrient approach through WPS provision to address negative nitrogen balance and achieve the high DPI recommendations for CAPD patients. However, additional calorie supplementation is warranted in patients with suboptimal energy intakes.

Funding sources

This investigator-initiated research did not receive any funding from public, commercial, or not-for-profit sectors. The supplement

was sourced from Aspen Sarl Sdn. Bhd., Selangor, Malaysia. Aspen Sarl Sdn. Bhd. had no part in study design, data collection and interpretation as well as manuscript writing.

Conflict of interest

The authors declare that they do not have conflict of interest.

Statement of authorship

SS, CHS, SHN and KBH performed data acquisition; SS, CHS, SHN and TK interpreted data, statistical analysis and wrote the manuscript; GBL, AH, SB and AG contributed to manuscript revision; SS and TK designed the study. All authors have read and approved the final version of the manuscript.

Acknowledgement

We would like to thank the nursing staff and patients of all participating hospitals for their support in this research. We also appreciate Dr Sreelakshmi Prem Ananthan for proof reading and evaluating this manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnesp.2018.04.002.

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