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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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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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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