International Urology and Nephrology
https://doi.org/10.1007/s11255-020-02768-5

NEPHROLOGY - ORIGINAL PAPER

Effectiveness of renal-specific oral nutritional supplements compared with diet counseling in malnourished hemodialysis patients

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Received: 3 August 2020 / Accepted: 21 December 2020

Abstract

Background Malnutrition is highly prevalent and a consequence of inflammation and related comorbidities among patients on maintenance hemodialysis. Oral nutritional supplementation (ONS) is recommended for malnourished patients with kidney failure. The study aimed to evaluate renal-specific oral nutrition (ONCE dialyze) supplement on nutritional status in patients on hemodialysis.

Methods Patients were randomized into 3 groups; treatment groups received 370 kcal/day of ONCE Dialyze ($N=26$) or 370 kcal/day of NEPRO ($N=30$) for 30 days. The control group ($N=24$) received no intervention. All patients were counseled by the same registered dietitian during the study. The nutritional status was evaluated using malnutrition inflammation score (MIS) assessment, body compositions, serum albumin and pre-albumin levels at baseline and 30 days.

Results Eighty patients were analyzed with mean age of 57.2 ± 15.9 years. The intervention group exhibited significant improvements in energy, protein, fat, fiber and magnesium intake by dietary interview compared with the control group. Percentage of changes in MIS was − 29.0% (95% CI − 40.5 to − 17.4), − 23.9% (95% CI − 37.2 to − 10.6) and 12.1% (95% CI − 19.2 to 43.4) for the ONCE dialyze, NEPRO and control groups, respectively (overall $P=0.006$). Percentage of changes in serum albumin was 5.3% (95% CI 1.9–8.7), 3.3% (95% CI − 0.1 to 6.7) and − 0.8% (95% CI − 4.3 to 2.7) for the ONCE dialyze, NEPRO, and control groups, respectively (overall $P=0.039$; $P=0.043$ for ONCE dialyze vs. control). No serious adverse effects were reported in any group.

Conclusion Dietary advice combined with ONS especially ONCE dialyze was associated with improved MIS, serum albumin, dietary energy and macronutrient intake among patients with kidney failure on maintenance hemodialysis.

Clinical trial registration TCTR20200801001.

Keywords Renal-specific oral nutrition · Maintenance hemodialysis · Serum albumin · Nutrition status

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Published online: 16 January 2021

Background

Patients with kidney failure undergoing chronic maintenance hemodialysis have high morbid and mortality rates, potentially reflecting a chronic inflammatory state and malnutrition [1]. Malnutrition is highly prevalent among patients with kidney failure on maintenance hemodialysis. The underlying mechanisms of malnutrition inflammation syndrome are complex, but metabolic derangements are related to both exaggerated protein degradation and suboptimal dietary protein and energy intake [2, 3]. Oral nutritional supplements (ONS) during hemodialysis may reduce the risk of mortality among these patients.

Dietary protein and energy intake were often lower than the recommendations for patients with kidney failure, especially on dialysis treatment days compared with non-dialysis treatment days [4, 5]. Hemodialysis units have offered nutritional supplements during hemodialysis and observational studies demonstrated that ONS improved serum albumin and nutritional status [6, 7] and was associated with reduced hospital readmission and mortality among patients undergoing in-center maintenance hemodialysis [8–11]. Very-low-quality evidence from a meta-analysis of randomized clinical trials suggests that short-term ONS improves nutritional status among patients with undergoing hemodialysis [12]. Appropriate ONS to facilitate intake of needed nutrients appears to be a reasonable strategy; these supplements exhibit high caloric density and protein content with reduced potassium, sodium and phosphorus content and do not require preparation [13]. Renal-specific supplements for hemodialysis are expected to improve energy intake and nutrition status without producing significant electrolyte abnormality [14]. No consensus has been reached and strong evidence remains lacking concerning the specific type of oral nutrition supplements and dietary approaches mentioned [15, 16]. This study aimed to evaluate oral renal-specific nutritional supplementation with ONCE Dialyze or NEPRO concerning nutrition status, inflammatory markers such as malnutrition inflammation score (MIS) and serum albumin level among patients on maintenance hemodialysis simultaneously receiving dietary advice for 30 days.

Methods

Study design and patient characteristics

This study employed a randomized controlled trial design among patients with kidney failure on maintenance hemodialysis at the hemodialysis center in Chaiyaphum, Thailand. All patients were recruited from the outpatient center, examined by the same physician and counseled by the same registered dietitian during the study. Only patients, who signed a written consent form, were included in the study. Permission for the study was obtained from the Local Ethics Committee of the Phramongkutklao Hospital and College of Medicine Ethics Committee for Human Research and conducted in accordance with the Declaration of Helsinki.

Inclusion criteria for this study included age 18–75 years, regular hemodialysis treatment for four hours, three times weekly for ≥ 3 months, malnourished conditions defined as serum albumin concentration < 3.8 g/dL, energy intake < 25 kcal/kg/day, protein intake < 1 g/kg/day, written informed consent and ability to understand the study protocol. Patients were excluded having inadequate dialysis, a life expectancy less than six months, non-adherence to dialysis regimen, active infection, malignancy and severe heart, lung or liver disease.

We randomly assigned patients in a 1:1:1 ratio in three groups. Patients in group 1 received 370 kcal sachets of ONCE dialyze (Thai Otsuka Pharmaceutical Co., Ltd. Thailand) for 30 days. Those in group 2 received 370 kcal sachets of NEPRO (Abbott Laboratories Altavista, VA, US) for 30 days. Patients in group 3 as the control group received no intervention. The components of ONCE dialyze and NEPRO supplements containing proteins, carbohydrates with fiber, fat, electrolytes and micronutrient are shown in Table 1. Participants were visited at each dialysis session to assess their adherence and were asked to return the empty ONS sachets to receive the next set of ONS sachets. meals during dialysis combined with lanthanum carbonate or a low-protein (< 1 g protein and < 20 mg phosphorus) meal during dialysis.

In the hemodialysis center, all patients at the beginning of dialysis treatment received dietary recommendations. All patients were interviewed, physically examined and investigated for any underlying medical illness. A dietitian advised patients on dialysis to maintain dietary intake within the recommended target every week in dialysis session.

Outcomes

We assessed the nutritional status of patients using MIS, anthropometric and biochemical measurements at the beginning of the study and after 30 days of intervention. The MIS was a scoring system for the assessment of malnutrition and inflammation. The MIS had 10 components derived from medical history, physical examination, BMI and laboratory parameters. Each component of the score is classified according to four levels of severity, ranging from 0 (normal) to 3 (severely abnormal). The sum of all 10 components of the MIS ranges from 0 (normal) to 30 (severe degree of malnutrition and inflammation). Higher MIS indicates a more severe degree of malnutrition and inflammation [17].

Table 1 Comparison of ONCE dialyze formula and other commercial dietary supplements per serving (370 kcal)

Component	ONCE dialyze	NEPRO
Caloric distribution of macronutrients (%)		
Protein	18%	18%
Carbohydrate	42%	35%
Fat	40%	47%
Source		
Protein	16.98 g	16.63 g
	Whey protein isolate 5 g (29.45%)	Milk protein 4.55 g (27.34%)
	Casein 11.98 g (70.55%)	Casein 12.08 g (72.66%)
Carbohydrate	41.19 g	33 g
	Maltodextrin 13.70 g (33.26%)	Cornmaltodextrin 21.12 g (64.02%)
	Isomaltulose 22.49 g (54.6%)	Sucrose 5.23 g (15.86%)
	Fibersol 2.25 g (5.46%)	Fibersol 4.11 g (12.46%)
	FOS 2.75 g (6.68%)	FOS 2.52 g (7.65%)
Fat	16.45 g	19.76 g
	Canola oil 4 g (24.32%)	HOSO 13.80 g (69.86%)
	HOSO 2 g (12.16%)	Canola oil 5.96 g (30.14%)
	MCT oil 5.25 g (31.91%)	
	Rice bran oil 5.20 g (31.61%)	
Micronutrient		
Vitamins and minerals		
Vitamin A (IU)	70.37	652.94
Vitamin D (IU)	3.18	17.43
Vitamin C (mg)	37.48	21.76
Calcium, mg	149.89	217.63
Phosphorus, mg	149.89	148.00
Magnesium, mg	40.81	43.51
Potassium, mg	206.20	217.63
Sodium, mg	154.40	217.63
Carnitine, mg	104.08	54.83
Others	As Thai RDI recommend	

FOS fructooligosaccharide, *HOSO* high oleic safflower oil, *MCT* medium-chain triglyceride, *ONCE* Otsuka Nutrition Pharmaceutical, *RDI* reference daily intake

Blood samples were taken from each patient just before the onset of the HD session at the beginning and end of the treatment phase. After centrifugation, serum was separated and stored. Serum albumin, pre-albumin, transferrin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, electrolyte, magnesium, phosphorus, calcium, serum urea nitrogen, creatinine, and hemoglobin were measured at baseline and the end of study. Any adverse event during study was recorded.

Body composition was evaluated using direct segmental multi-frequency bioelectrical impedance analysis (DSM-BIA, In-Body (720) body compositions analyzer). The spectrum of electrical frequencies was used to predict the body composition, total fat mass, total body water and percentage of body fat in the various body segments. Body composition was assessed at baseline and at the end of the study after the long interdialytic period. Subjects also underwent muscle strength assessment using the hand grip test. The hand grip strength was measured with the patient seated with the elbow flexed at 90° and the forearm in the neutral position by mechanical dynamometer [18]. Three measurements were taken and the best reading was noted for the study. Anthropometric measurements were done in all patients. Triceps skinfold thickness was done with calipers and mid-arm circumference was measured with a stretchable tape.

Dietary recalls for dialysis and non-dialysis days were reviewed by a registered dietitian before and after the study period and analyzed for nutrition composition using the standard national food database program (Inmucal, Version 3.2). All subjects agreed to take part in a self-assessed health-related quality of life using the SF-36 questionnaire containing eight domains divided into two parts: Physical Health (physical functioning, role limitations due to physical

health, bodily pain, and general health) and Mental Health (vitality, social functioning, role limitations due to emotional problems, and mental health) [19].

Statistical analysis

Data were analyzed using the statistical package for social sciences (SPSS), Version 16.0, Chicago, IL, USA). Each value was expressed as percentage, mean ± SD or mean change with 95% confidence interval (CI). Continuous variables between baseline and at the end of study were compared using paired *t* tests and Wilcoxon signed ranks test. Chi-square test was used to examine the categorical variables. Values and changes in study parameters were compared among the three groups using an analysis of variance model with Scheffe post hoc test and repeated measures ANOVA. For all statistical tests, significance was considered as $P < 0.05$.

Results

We reviewed the eligibility criteria of 142 patients; 95 patients were included and 86 patients were randomized in three groups. Patients received diet counseling in the control ($N = 24$), NEPRO supplement (N-30) and ONCE dialyze supplement groups ($N = 26$) as shown in the flow diagram (Fig. 1). The patients were all Thais with mean age 57.2 ± 15.9 years, median dialysis vintage 3.5 ± 1.8 years, and mean single pool KT/V was 1.6 ± 0.4. The overall nutritional status is shown in Table 2 including MIS (6.5 ± 3.3), serum albumin level (3.5 ± 0.5 g/dL), pre-albumin (0.3 ± 0.1 mg/dL), body mass index (BMI) (23.2 ± 4.5 kg/m^2), estimated energy intake (19.8 ± 6.6 kcal/kg/day) and estimated protein intake (0.8 ± 0.3 g/kg/day) at baseline. The comorbid diseases among the patients included diabetes mellitus (61.3%), hypertension (81.3%) and dyslipidemia (40%). At baseline, the three groups did not differ significantly regarding demographic, clinical, laboratory, dietary calorie or macronutrient values (Table 2), except significantly higher patients with diabetes mellitus was found in the NEPRO group.

Changes of energy and nutrient intake

Table 3 shows the change for estimated energy and nutrient intake at baseline and end of study. Estimated energy, protein, fat, fiber and magnesium intake increased significantly in the ONCE dialyze and NEPRO groups, but no significant change was observed in the control group. When changes in these outcomes were compared among the three groups, a statistically significant difference was

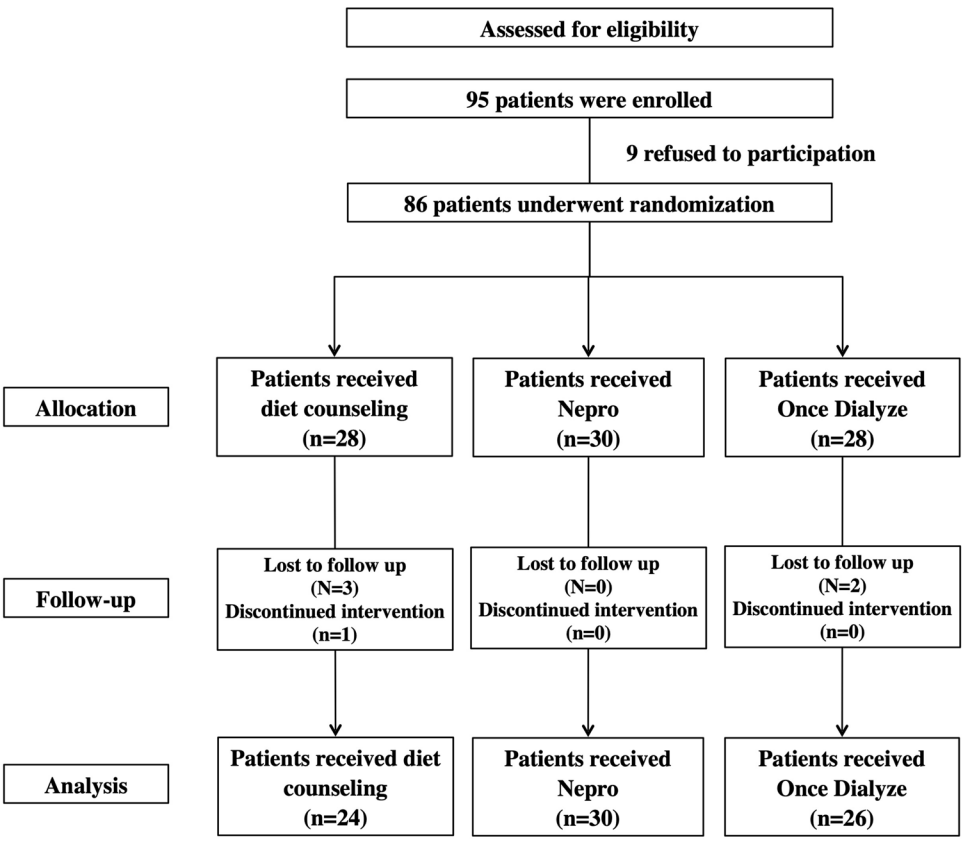

Fig. 1 Flow of clinical study

Table 2 Baseline characteristics of the study population

	Control ($n=24$)	NEPRO ($n=30$)	ONCE Dialyze ($n=26$)	P value
Age (years)	57.2 ± 15.9	53.0 ± 10.3	57.2 ± 9.7	0.414
Duration of dialysis (years)	3.5 ± 1.8	2.5 ± 1.5	3.0 ± 1.8	0.121
Hypertension	18 (75)	26 (86.7)	21 (80.8)	0.553
Dyslipidemia	9 (37.5)	13 (43.3)	10 (38.5)	0.893
Type 2 diabetes	10 (41.7)	23 (76.7)	16 (61.5)	0.032
Clinical parameters				
Body weight (kg)	56.9 ± 14.5	56.5 ± 12.5	59.1 ± 9.9	0.669
Body mass index (kg/m^2)	23.3 ± 5.1	23.6 ± 4.0	22.7 ± 4.6	0.749
Percentage of body fat (%)	25.7 ± 10.0	25.8 ± 11.6	28.5 ± 10.3	0.640
Muscle mass (kg)	39.9 (34.3, 44.1)	37.4 (33.5, 44.6)	38.8 (35.8, 43.8)	0.445
Mid-arm circumference (cm)	28.9 ± 5.9	27.5 ± 4.8	28.7 ± 3.4	0.540
Triceps skinfold thickness (mm)	28.3 ± 11.8	30.5 ± 9.3	31.5 ± 9.9	0.585
Hand grip test (kg)	16.9 ± 9.0	14.5 ± 4.3	17.2 ± 6.5	0.303
Total SF36	60.1 ± 20.2	54.5 ± 24.1	48.8 ± 20.9	0.333
Total MIS	6.0 ± 2.6	6.7 ± 4.1	6.7 ± 3.8	0.770
Laboratory findings				
Single pool Kt/V	1.7 ± 0.4	1.6 ± 0.4	1.6 ± 0.3	0.648
Blood urea nitrogen (mg/dL)	43.9 ± 18.6	41.6 ± 15.9	42.7 ± 16.0	0.881
Serum creatinine (mg/dL)	7.7 ± 3.0	7.4 ± 2.6	7.6 ± 2.9	0.936
Estimated GFR (ml/min/1.73m^2)	6.9 ± 3.2	6.9 ± 2.8	6.9 ± 2.9	0.995
Sodium (mEq/L)	137.7 ± 3.2	136.7 ± 4.0	137.1 ± 3.3	0.630
Potassium (mEq/L)	4.3 ± 0.8	4.3 ± 0.7	4.2 ± 0.6	0.880
Chloride (mEq/L)	96.5 ± 4.0	94.7 ± 3.3	95.2 ± 2.6	0.125
Bicarbonate (mEq/L)	30.8 ± 6.6	30.3 ± 3.5	30.1 ± 3.7	0.893
Calcium (mg/dL)	9.3 ± 0.6	9.3 ± 1.2	9.2 ± 0.7	0.925
Phosphorus (mg/dL)	3.7 ± 1.4	3.7 ± 1.5	3.9 ± 1.8	0.928
Magnesium (mg/dL)	2.5 ± 0.7	2.3 ± 0.5	2.4 ± 0.9	0.791
Fasting plasma glucose (mg/dL)	108.4 ± 31.2	113 ± 53.5	134.8 ± 98.6	0.424
Prealbumin (mg/L)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.429
Albumin (g/dL)	3.53 ± 0.26	3.55 ± 0.24	3.57 ± 0.22	0.896
AST (U/L)	21.0 ± 9.3	23.3 ± 11.9	20.5 ± 6.6	0.507
ALT (U/L)	11.5 (8.5, 24)	15 (9, 28)	13 (10, 17)	0.425
Dietary intake per day				
Energy (kcal/day)	1170.0 ± 270.8	1066.5 ± 247.8	1070.9 ± 287.4	0.389
Energy (kcal/kg/day)	21.6 ± 6.6	19.7 ± 6.7	18.5 ± 6.3	0.326
Protein (g/day)	50.2 ± 11.7	43.3 ± 11.2	44.9 ± 14.1	0.183
Protein (g/kg/day)	0.9 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.147
Carbohydrate (g/day)	187.8 ± 57.0	168.7 ± 44.3	171.1 ± 54.5	0.443
Fat (g/day)	24.2 ± 12.6	24.3 ± 10.8	22.9 ± 10.7	0.910
Dietary fiber (g/day)	4.9 ± 2.5	5.3 ± 3.4	5.7 ± 2.9	0.782
Phosphorus (mg/day)	425.1 ± 137.1	447.1 ± 230.2	431.3 ± 153.7	0.919
Potassium (mg/day)	1044.5 ± 318.8	960.9 ± 401.4	952.0 ± 277.2	0.642
Sodium (mg/day)	1857.3 ± 748.6	1671.8 ± 699.9	1799.9 ± 788.6	0.702
Calcium (mg/day)	204.6 ± 135.3	185.7 ± 98.4	184.4 ± 93.7	0.562
Magnesium (mg/day)	25 (18.3,36.9)	26.6 (15.8,45.2)	35.5 (16.2,52.0)	0.838

Values presented as n (%), mean ± SD and median with IQR. Parameters are compared among three groups using Chi-square test, analysis of variance model or Kruskal–Wallis test

Table 3 Change of dietary intake between groups

	Control ($n=24$)	NEPRO ($n=30$)	ONCE dialyze ($n=26$)	P value
Dietary intake				
Energy (kcal/day)				0.003
Baseline	1170.0 ± 270.8	1066.5 ± 247.8	1070.9 ± 287.4	
End of study	1213.9 ± 323.9	1418.7 ± 242[a,c]	1453.9 ± 383[a,c]	
Energy (kcal/kg/day)				0.014
Baseline	21.6 ± 6.6	19.7 ± 6.7	18.5 ± 6.3	
End of study	22.9 ± 8.3	25.8 ± 7.6[a,c]	24.7 ± 6.5[a,c]	
Protein (g/day)				< 0.001
Baseline	50.2 ± 11.7	43.3 ± 11.2	44.9 ± 14.1	
End of study	53.6 ± 11.6	61.3 ± 12.1[a,c]	66 ± 17.8[a,c]	
Protein (g/kg/day)				< 0.001
Baseline	0.9 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	
End of study	1 ± 0.3	1.1 ± 0.3[a,c]	1.1 ± 0.3[a,c]	
Carbohydrate (g/day)				0.232
Baseline	187.8 ± 57.0	168.7 ± 44.3	171.1 ± 54.5	
End of study	183.4 ± 57.1	189.9 ± 44.7	198.6 ± 59.2	
Fat (g/day)				< 0.001
Baseline	24.2 ± 12.6	24.3 ± 10.8	22.9 ± 10.7	
End of study	29.6 ± 13.8	46.7 ± 12.8[a,b,c]	45.2 ± 15.9[a,c]	
Dietary fiber (g/day)				< 0.001
Baseline	4.9 ± 2.5	5.3 ± 3.4	5.7 ± 2.9	
End of study	5.6 ± 3.6	7.8 ± 3.3[a,c]	10.3 ± 3.4[a,b,c]	
Phosphorus (mg/day)				0.256
Baseline	425.1 ± 137.1	447.1 ± 230.2	431.3 ± 153.7	
End of study	503.8 ± 178.7	576.3 ± 147.9[a]	596.5 ± 187.7[a]	
Potassium (mg/day)				0.085
Baseline	1044.5 ± 318.8	960.9 ± 401.4	952.0 ± 277.2	
End of study	1111.9 ± 388.8	1217.7 ± 303.3[a]	1263.5 ± 526[a]	
Sodium (mg/day)				0.333
Baseline	1857.3 ± 748.6	1671.8 ± 699.9	1799.9 ± 788.6	
End of study	1882.3 ± 697.4	2046.6 ± 783.5[a]	1865.6 ± 938.8	
Calcium (mg/day)				0.208
Baseline	204.6 ± 135.3	185.7 ± 98.4	184.4 ± 93.7	
End of study	299.7 ± 171.4	368.7 ± 103.2	358.3 ± 140.9	
Magnesium (mg/day)				< 0.001
Baseline	25.0 (18.3,36.9)	26.6 (15.8,45.2)	35.5 (16.2,52.0)	
End of study	18 (12.9,34.2)	69.3 (60.2,89.3)[a,c]	65 (56,90.2)[a,c]	

Values for each group represented the mean and standard deviation. P values of the main effect and interaction effect were given by repeated measure ANOVA

[a] P value of < 0.05 was defined as statistical significance used to compare two time points (baseline and end of study) within group

[b] P value < 0.05 was used to compare the main effect between control groups

[c] P value < 0.05 was used to compare the mean difference between control groups by multiple comparison test in the analysis of variance

seen ($P < 0.05$; Table 3). Significantly improved percentage of mean changes in estimated energy and nutrient intake are also shown in Fig. 2. Changes in other estimated nutrient intake did not significantly differ among groups.

Changes of MIS and nutritional status

MIS is a scoring system which strongly correlates with mortality, nutrition and inflammation among patients on dialysis.

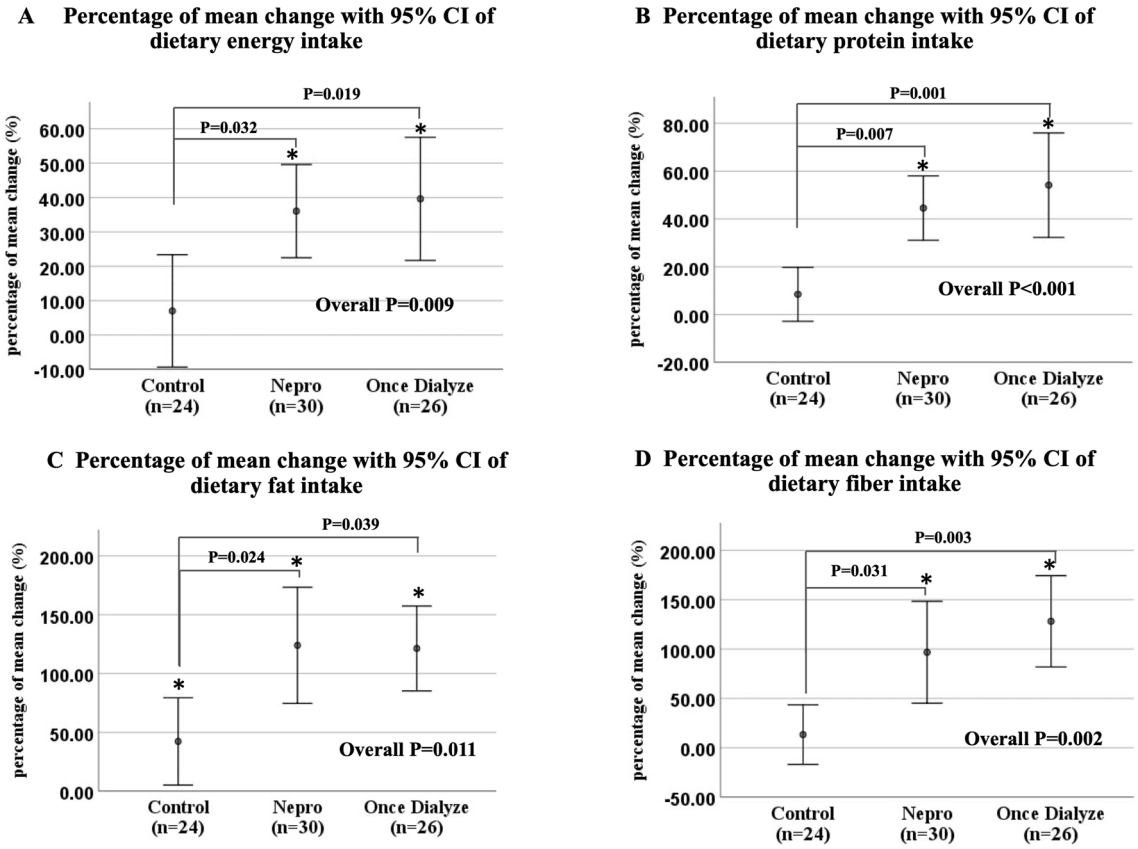

Fig. 2 Percentage of mean changes with 95% CI in dietary intake with three-day food record after nutritional intervention. Values are presented as percentage of mean change with 95% CI. $^{*}P$ value < 0.05 compared with baseline by Paired *t* test

MIS is one of the reliable methods to assess nutritional status of patients on dialysis, and MIS was used to more clearly identify effects of ONS on nutritional status. Total MIS decreased significantly among patients in the ONCE dialyze and NEPRO groups, but exhibited no significant change in the control group, while a significant difference ($P = 0.029$) was found among the three groups (Table 4). Percentage of mean changes in MIS also significantly improved in the ONCE dialyze [− 29.0% (95% CI − 40.5 to − 17.4)] and NEPRO [− 23.9% (95% CI − 37.2 to − 10.6)] groups, compared with the control, [12.1% (95% CI − 19.2 to 43.4)] (overall $P = 0.006$; $P = 0.012$ for ONCE dialyze vs. control and $P = 0.023$ for NEPRO vs. control, Fig. 3).

Additionally, serum albumin concentration increased significantly in the ONCE dialyze group, whereas no significant change was found in the control and NEPRO groups. Significant differences in change of serum albumin levels were observed in the ONCE dialyze group [0.18 (95% CI 0.07–0.28)] when compared with the control group [− 0.04 (95% CI − 0.17 to 0.09)] ($P = 0.031$; Table 4). Percentage of changes in serum albumin was 5.3% (95% CI 1.9–8.7), 3.3% (95% CI − 0.1 to 6.7) and − 0.8% (95% CI − 4.3 to 2.7) for the ONCE dialyze, NEPRO, and control groups, respectively (overall $P = 0.039$; $P = 0.043$ for ONCE dialyze vs. control, Fig. 3).

Change of serum pre-albumin (0.02 mg/dL, 95% CI 0.002–0.04) and percentage of change serum pre-albumin (8.5%, 95% CI 1.4–15.5) significantly increased after ONCE dialyze supplement, but no significant change was found among the three groups (Table 4; Fig. 3). Body weight, BMI, mid-arm circumference and BUN showed significant increases in the intervention groups, but these parameters did not significantly differ among groups (Table 4). No significant change was observed between groups by treatment effects regarding anthropometric measurements, body composition or physical function (Table 4).

During the study, no serious adverse events were observed especially electrolyte disturbances and fluid overload. Changes in serum electrolytes and minerals did not significantly differ among groups. One patient in the ONCE dialyze group, and two patients in the NEPRO group presented mild nausea, vomiting and diarrhea. At the study's completion, patient compliance, receiving the ONS on schedule, was 96.0% and overall outcomes at the end study are demonstrated in Table 5.

Table 4 Change of nutritional parameters and biochemical profiles between groups

	Control ($n=24$)	NEPRO ($n=30$)	ONCE dialyze ($n=26$)	Group*time *P* value
Clinical parameters				
Body weight (kg)				0.236
Baseline	56.9 ± 14.5	56.5 ± 12.5	59.1 ± 9.9	
End of study	56.9 ± 14.8	57.1 ± 12.3[a]	59.8 ± 9.9[a]	
Body mass index (kg/m^2)				0.257
Baseline	23.3 ± 5.1	23.6 ± 4.0	22.7 ± 4.6	
End of study	23.4 ± 5.2	22.9 ± 4.6[a]	23.9 ± 4.1[a]	
Percentage of body fat (%)				0.223
Baseline	25.7 ± 10.0	25.8 ± 11.6	28.5 ± 10.3	
End of study	23.5 ± 12.4	27.1 ± 10.2	26 ± 11.8	
Muscle mass (kg)				0.396
Baseline	39.6 ± 7.6	39.4 ± 8.2	40.0 ± 6.8	
End of study	40.6 ± 8.5	39.3 ± 8	41.4 ± 8.1	
Mid-arm circumference (cm)				0.197
Baseline	28.9 ± 5.9	27.5 ± 4.8	28.7 ± 3.4	
End of study	28.9 ± 5.6	28.2 ± 5[a]	29.3 ± 3.2[a]	
Triceps skinfold thickness (mm)				0.991
Baseline	28.3 ± 11.8	30.5 ± 9.3	31.5 ± 9.9	
End of study	28.2 ± 11.2	30.6 ± 9.6	31.7 ± 8.5	
Hand grip test (kg)				0.502
Baseline	16.9 ± 9.0	14.5 ± 4.3	17.2 ± 6.5	
End of study	17 ± 7.8	15.4 ± 4.9[a]	18.5 ± 8.1	
Total SF36				0.307
Baseline	60.1 ± 20.2	54.5 ± 24.1	48.8 ± 20.9	
End of study	60.6 ± 25	64.4 ± 22.1[a]	55.4 ± 23.3	
Individual MIS score				
Medical history				0.031
Baseline	3.0 ± 1.6	3.2 ± 2.3	3.7 ± 2.2	
End of study	2.8 ± 2.1	2.0 ± 1.3[a]	1.8 ± 0.9[a,c]	
Physical exam				0.241
Baseline	0.9 ± 1.0	1.2 ± 1.14	0.9 ± 0.9	
End of study	0.8 ± 1.0	0.6 ± 0.9 [a]	0.6 ± 0.9[c]	
Body mass index (kg/m^2)				0.580
Baseline	0.4 ± 0.6	0.4 ± 0.6	0.2 ± 0.7	
End of study	0.3 ± 0.5	0.4 ± 0.6	0.1 ± 0.7	
Laboratory parameters				0.035
Baseline	1.7 ± 1.2	1.9 ± 1.5	1.9 ± 1.3	
End of study	2.2 ± 1.0	1.6 ± 1.2	1.5 ± 0.9	
Total MIS				0.029
Baseline	6.0 ± 2.6	6.7 ± 4.1	6.7 ± 3.8	
End of study	5.9 ± 3.2	4.6 ± 2.7[a]	4.1 ± 1.8[a,c]	
Laboratory findings				
Blood urea nitrogen (mg/dL)				0.650
Baseline	43.9 ± 18.6	41.6 ± 15.9	42.7 ± 16.0	
End of study	57.6 ± 21.7[a]	59.6 ± 21.8[a]	61 ± 16.8[a]	
Serum creatinine (mg/dL)				0.908
Baseline	7.7 ± 3.0	7.4 ± 2.6	7.6 ± 2.9	
End of study	8.3 ± 2.4	8.1 ± 3.8	8.1 ± 3.1	
Sodium (mEq/L)				0.341
Baseline	137.7 ± 3.2	136.7 ± 4.0	137.1 ± 3.3	

Table 4 (continued)

	Control ($n=24$)	NEPRO ($n=30$)	ONCE dialyze ($n=26$)	Group*time *P* value
End of study	142 ± 20.8	136.8 ± 4.9	137.1 ± 3.6	
Potassium (mEq/L)				0.516
Baseline	4.3 ± 0.8	4.3 ± 0.7	4.2 ± 0.6	
End of study	4.2 ± 0.7	4.4 ± 0.9	4.3 ± 0.6	
Chloride (mEq/L)				0.877
Baseline	96.5 ± 4.0	94.7 ± 3.3	95.2 ± 2.6	
End of study	97 ± 3.3	94.8 ± 4.7	95 ± 3.1	
Bicarbonate (mEq/L)				0.310
Baseline	30.8 ± 6.6	30.3 ± 3.5	30.1 ± 3.7	
End of study	26.8 ± 3.2[a]	27.4 ± 3.3[a]	27.9 ± 3.5[a]	
Calcium (mg/dL)				0.537
Baseline	9.3 ± 0.6	9.3 ± 1.2	9.2 ± 0.7	
End of study	8.7 ± 1.1[a]	8.9 ± 1.3	8.5 ± 1.2[a]	
Phosphorus (mg/dL)				0.444
Baseline	3.7 ± 1.4	3.7 ± 1.5	3.9 ± 1.8	
End of study	3.7 ± 1.5	4.1 ± 1.8	4.3 ± 1.5[a]	
Magnesium (mg/dL)				0.866
Baseline	2.5 ± 0.7	2.3 ± 0.5	2.4 ± 0.9	
End of study	2.5 ± 0.6	2.6 ± 0.7[a]	2.6 ± 0.7	
Fasting plasma glucose (mg/dL)				0.174
Baseline	108.4 ± 31.2	113 ± 53.5	134.8 ± 98.6	
End of study	115.6 ± 36.62	114.6 ± 71.4	148.1 ± 96.2	
Prealbumin (mg/dL)				0.514
Baseline	0.28 ± 0.06	0.31 ± 0.08	0.29 ± 0.08	
End of study	0.28 ± 0.09	0.32 ± 0.10	0.31 ± 0.08[a]	
Albumin (g/dL)				0.031
Baseline	3.5 ± 0.3	3.6 ± 0.2	3.6 ± 0.2	
End of study	3.7 ± 0.4	3.8 ± 0.6	3.9 ± 0.5[a,c]	
AST (U/L)				0.250
Baseline	21.0 ± 9.3	23.3 ± 11.9	20.5 ± 6.6	
End of study	21 ± 12.3	21.4 ± 8	22.4 ± 9	
ALT (U/L)				0.240
Baseline	11.5 (8.5, 24)	15 (9, 28)	13 (10, 17)	
End of study	12 (8, 20.5)	14 (10, 18)	15 (12, 19)	

Values for each group represented the mean and standard deviation. *P* values of the main effect and interaction effect were given by repeated measure ANOVA

[a]*P* value of < 0.05 was defined as statistical significance used to compare two time points (baseline and end of study) with in group by Bonferroni multiple comparison test

[b]*P* value < 0.05 was used to compare the main effect between control groups

[c]*P* value < 0.05 was used to compare the mean difference between control groups by multiple comparison test in the analysis of variance

Discussion

Administration of ONS represents the first step of nutritional intervention when dietary counseling aimed at increasing spontaneous intake of nutrients fails. This randomized controlled trial investigated the effects of renal-specific ONS among patients with kidney failure undergoing maintenance hemodialysis. Our results supported the use of ONCE dialyzed and NEPRO supplement to improve total MIS, energy, protein, fat, fiber and magnesium intake without significant influence on serum electrolytes among patients with kidney failure receiving hemodialysis. Our finding is consistent with a related meta-analysis [12]. We also demonstrated improvements in serum albumin after 30 days of receiving ONCE dialyzed supplement.

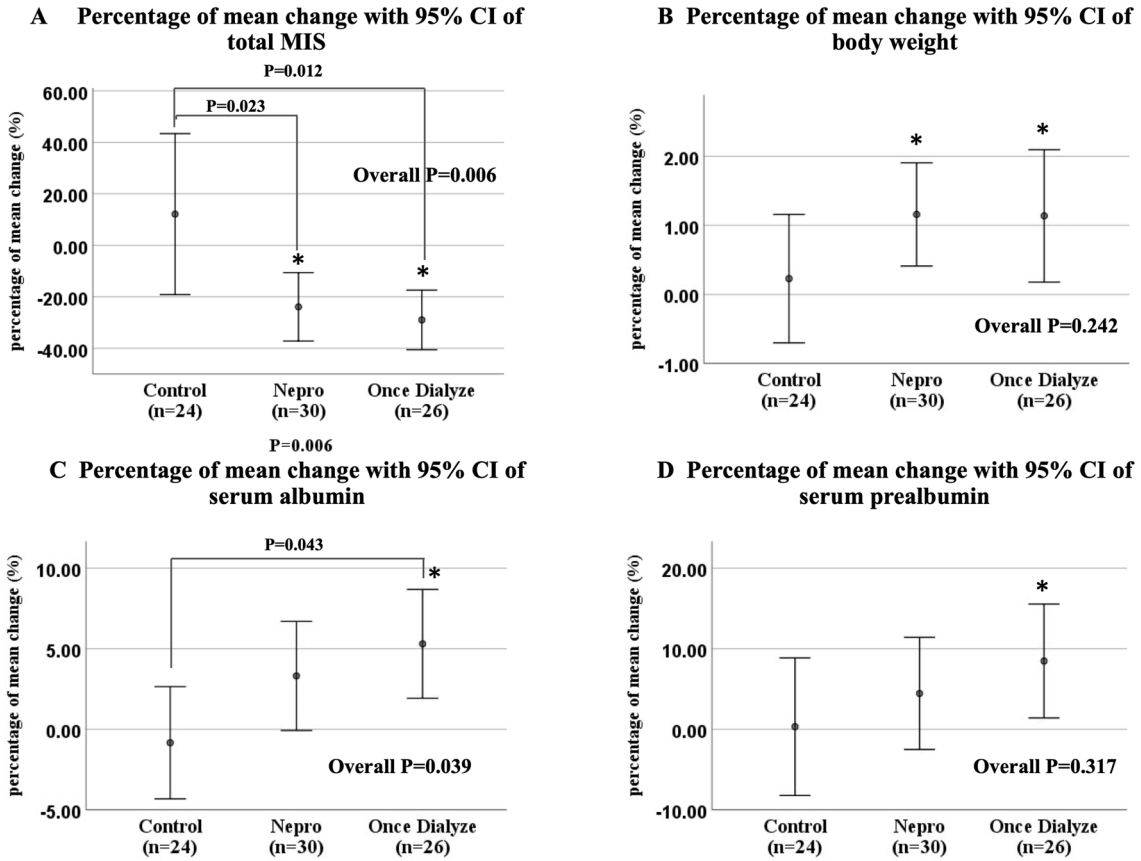

Fig. 3 Percentage of mean changes with 95% CI in total MIS, body weight, serum albumin and pre-albumin after nutritional intervention. Values are presented as percentage of mean change with 95% CI. *P value < 0.05 compared with baseline

Malnutrition is highly prevalent among patients with kidney failure undergoing dialysis, which is associated with increased mortality risk among patients on dialysis [11]. One of the most important causes of malnutrition inflammation complex syndrome is loss of appetite with low dietary protein and energy intake [20]. Clinical studies from retrospective and cohort studies have indicated that nutritional interventions were associated with improved mortality and morbidity among patients undergoing dialysis patient, but large randomized clinical trials remain limited [21]. Several epidemiological studies have indicated that improved nutritional status parameters were associated with improved survival among patients undergoing dialysis [1]. Additionally, ONS significantly improved the quality of life during interventions [22–24]. Our study indicated that the renal-specific diet supplement significantly improved total MIS, energy, protein and fiber intake and maintained nutritional markers among patients with kidney failure undergoing maintenance hemodialysis. This study was consistent with other studies demonstrating effectiveness of dietary intervention on nutritional biomarkers among patients with kidney failure undergoing maintenance hemodialysis [25, 26]. Therefore, additional long-term well-designed studies are needed to be conducted concerning the efficacy of specific renal supplements among malnourished patients with kidney failure undergoing maintenance hemodialysis.

Causes of malnutrition inflammation complex syndrome during hemodialysis include an imbalance between pro- and anti-oxidant system [27]. As MIS is a reliable method to assess chronic inflammation and malnutrition among patients undergoing dialysis. Moreover, evaluating the nutritional status of patients on maintenance hemodialysis using MIS can determine patient outcomes [17]. Our study confirmed that renal-specific diet supplement improved nutritional score from the calculated MIS among patients with kidney failure undergoing maintenance hemodialysis. The improvement in dietary energy and protein intake has anabolic, anti-inflammatory and anti-oxidative effects on nutritional status among patients with kidney failure. This finding was consistent with related studies of improved inflammatory markers, persistent anabolic benefits for muscle metabolism and physical function among patients on maintenance hemodialysis after intradialytic protein supplementation [22, 28, 29].

Table 5 Outcomes at the end of study between groups

	Control ($n=24$)	NEPRO ($n=30$)	ONCE dialyze ($n=26$)	P value
Dietary intake				
Energy (kcal/day)	1213.9 ± 323.9	1418.7 ± 242	1453.9 ± 383	0.044
Energy (kcal/kg/day)	22.9 ± 8.3	25.8 ± 7.6	24.7 ± 6.5	0.453
Protein (g/day)	53.6 ± 11.6	61.3 ± 12.1	66 ± 17.8[a]	0.025
Protein (g/kg/day)	1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.448
Carbohydrate (g/day)	183.4 ± 57.1	189.9 ± 44.7	198.6 ± 59.2	0.667
Fat (g/day)	29.6 ± 13.8	46.7 ± 12.8[a]	45.2 ± 15.9[a]	< 0.001
Dietary fiber (g/day)	5.6 ± 3.6	7.8 ± 3.3	10.3 ± 3.4[a]	< 0.001
Phosphorus (mg/day)	503.8 ± 178.7	576.3 ± 147.9	596.5 ± 187.7	0.207
Potassium (mg/day)	1111.9 ± 388.8	1217.7 ± 303.3	1263.5 ± 526	0.498
Sodium (mg/day)	1882.3 ± 697.4	2046.6 ± 783.5	1865.6 ± 938.8	0.713
Calcium (mg/day)	299.7 ± 171.4	368.7 ± 103.2	358.3 ± 140.9	0.240
Magnesium (mg/day)	18 (12.9, 34.2)	69.3 (60.2, 89.3)[a]	65 (56, 90.2)[a]	< 0.001
Clinical parameters				
Body weight (kg)	56.9 ± 14.8	57.1 ± 12.3	59.8 ± 9.9	0.690
Body mass index (kg/m^2)	23.4 ± 5.2	22.9 ± 4.6	23.9 ± 4.1	0.756
Percentage of body fat (%)	23.5 ± 12.4	27.1 ± 10.2	26 ± 11.8	0.607
Muscle mass (kg)	40.6 ± 8.5	39.3 ± 8	41.4 ± 8.1	0.686
Mid-arm circumference (cm)	28.9 ± 5.6	28.2 ± 5	29.3 ± 3.2	0.711
Triceps skinfold thickness (mm)	28.2 ± 11.2	30.6 ± 9.6	31.7 ± 8.5	0.495
Hand grip test (kg)	17 ± 7.8	15.4 ± 4.9	18.5 ± 8.1	0.313
Total SF36	60.6 ± 25	64.4 ± 22.1	55.4 ± 23.3	0.460
Total MIS	5.9 ± 3.2	4.6 ± 2.7	4.1 ± 1.8	0.106
Laboratory findings				
Blood urea nitrogen (mg/dL)	57.6 ± 21.7	59.6 ± 21.8	61 ± 16.8	0.832
Serum creatinine (mg/dL)	8.3 ± 2.4	8.1 ± 3.8	8.1 ± 3.1	0.956
Sodium (mEq/L)	142 ± 20.8	136.8 ± 4.9	137.1 ± 3.6	0.219
Potassium (mEq/L)	4.2 ± 0.7	4.4 ± 0.9	4.3 ± 0.6	0.736
Chloride (mEq/L)	97 ± 3.3	94.8 ± 4.7	95 ± 3.1	0.091
Bicarbonate (mEq/L)	26.8 ± 3.2	27.4 ± 3.3	27.9 ± 3.5	0.511
Calcium (mg/dL)	8.7 ± 1.1	8.9 ± 1.3	8.5 ± 1.2	0.448
Phosphorus (mg/dL)	3.7 ± 1.5	4.1 ± 1.8	4.3 ± 1.5	0.434
Magnesium (mg/dL)	2.5 ± 0.6	2.6 ± 0.7	2.6 ± 0.7	0.876
Fasting plasma glucose (mg/dL)	107 (89, 134.5)	120 (88, 193)	104 (94, 175)	0.179
Prealbumin (mg/dL)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.297
Albumin (g/dL)	3.7 ± 0.4	3.8 ± 0.6	3.9 ± 0.5	0.263
AST (U/L)	21 ± 12.3	21.4 ± 8	22.4 ± 9	0.870
ALT (U/L)	12 (8, 20.5)	14 (10, 18)	15 (12, 19)	0.695

Values represented mean ± SD and Median (IQR)

[a] P value < 0.05 was used to compare the mean or median between control groups by Scheffe post hoc test in the analysis of variance or Kruskal–Wallis test

Hypoalbuminemia is another marker reflecting nutritional status and a strong predictor of poor outcomes and mortality among patients on dialysis [30]. In our study, we found that serum albumin and pre-albumin in the ONCE dialyze group were significantly increased by 0.18 g/dL and 0.02 mg/L, respectively. The beneficial effects of ONCE dialyze with a high amount of protein (16.98 g/370 kcal) and 29.5% whey protein content on nutritional status might have been due to anabolic effects of whey protein and its branched-chain amino acid contents on stimulating protein synthesis, increasing muscle mass and ameliorating exercise injuries [31, 32]. Another study supported that whey protein constituted an anti-oxidant with anti-inflammatory properties that increased glutathione content and inhibited DNA damage [33]. However, soy and casein protein provide potentially less muscle protein synthesis than whey protein [34]. As a

consequence, our study found that oral ONCE Dialyze supplements with 29.5% whey protein isolate improved serum albumin levels among malnourished patients with kidney failure.

Our study found that oral ONCE Dialyze and NEPRO supplements had no significant effect on serum potassium and phosphorus level. Both renal-specific ONS supplement with low potassium and phosphorus content did not increase risk of electrolyte abnormalities among patients with kidney failure undergoing maintenance hemodialysis. Although our study showed a significant increase in dietary magnesium intake after ONS intervention, no significant change was observed in serum magnesium levels in the ONCE Dialyze and NEPRO groups. Moreover, compliance of patients in our study was extremely good; 96% of patients complied with the ONS supplement for 30 days, improving an average additional caloric intake with high amount of protein and fiber. The high percentage of compliance may reflect the type of patient selection in our study in that they received the intervention based on their excellent reputation for nutritional management. Therefore, the ONCE Dialyze supplement was convenient for educated patients with kidney failure on hemodialysis and unable to choose the most appropriate high protein renal diet with low sodium, phosphate and potassium to maintain adequate energy intake. However, patient compliance was limited by the relatively short period of follow-up.

Our study encountered several limitations. First, our study comprised a single-center study with a small sample size lacking any blinding of the interventions causing detection and performance bias. Second, the effects of ONS on serum albumin levels was observed in our study, but we could not determine the effects of ONS or a short-term increase in albumin level concerning the mortality risk among patients on dialysis. Third, the INMUCAL program could not represent all micronutrients completely, especially magnesium (validity 36.3%). Therefore, the amount of magnesium was shown lower than that of the usual diet. Finally, we could not evaluate the effects of ONS on inflammation, which is closely associated with treatment outcomes among patients with kidney failure.

In conclusion, short-term oral nutritional supplements using ONCE dialyze or NEPRO were associated with increased energy, protein, fat, fiber and magnesium intake. ONCE dialyze supplement significantly improved nutritional status score and serum albumin level in malnourished patients with kidney failure undergoing maintenance hemodialysis without abnormal electrolyte disturbance. Therefore, renal-specific formula might be regarded as a complementary supplement to the current therapeutic remedies for malnutrition among patients on hemodialysis. Further trials are required to confirm the long-term efficacy of renal-specific ONS particularly those involving the observation of morbidity and mortality risk among malnourished patients on hemodialysis.

Acknowledgements The authors wish to acknowledge the contributions of the following individuals to this study: staff in the Division of Nephrology in Phramongkutklao Hospital.

Funding The study was supported by a Grant from Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand and the Thai Otsuka Pharmaceutical Co., Ltd. Thailand, which had no influence on the design, conduct, analysis or reporting of our trial.

Data availability Data supporting this study are available upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval The study was approved by the Ethics Committee of the Institute Review Board at the Royal Thai Army Medical Department and was conducted according to the Declaration of Helsinki.

Informed consent Informed consent was obtained from all participants.

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