The effects of oral low-protein energy supplements on nutritional status in maintenance hemodialysis patients with protein-energy wasting: a prospective randomized controlled trial

doi: 10.6133/apjcn.202501/PP.0005
Published online: January 2025

Running title: Low-protein supplements in hemodialysis patients

Danhua Liang MD[1], Xianrui Dou MD, PhD[2], Luona Wen MS[3], Yongqian Liang MD[4], Wei Zhang BS[2], Lan Liu MD, PhD[4], Ke Chen MD[1], Rongshao Tan MD, PhD[3]

[1]Department of Nutrition, Shunde Hospital, Southern Medical University, The First People's Hospital of Shunde, Foshan, China.
[2]Department of Nephrology, Shunde Hospital, Southern Medical University, The First People's Hospital of Shunde, Foshan, China.
[3]Guangzhou Institute of Disease-Oriented Nutritional Research, Guangzhou Red Cross Hospital of Jinan University, Guangzhou, China.
[4]Department of Endocrinology and Metabolism, Shunde Hospital, Southern Medical University, The First People's Hospital of Shunde, Foshan, China.

Authors' email addresses and contributions:
Danhua Liang: 894940278@qq.com
Contribution:conceptualized and designed the study, collected the data, analyzed and interpreted the data,drafted the manuscript.

Xianrui Dou: betty9911@163.com
Contribution: contributed to the design of the study, assisted with data collection.

Luona Wen: wenluona@163.com
Contribution:provided statistical expertise in the data analysis and interpretation, revised the manuscript critically for important intellectual content.

Yongqian Liang:102LYQ@163.com
Contribution: revised the manuscript critically for important intellectual content.

Wei Zhang: sdfrancis@126.com
Contribution:undertook data collection.

Lan Liu: 1326716768@qq.com
Contribution: assisted with data collection.

Ke Chen: cocochen@smu.edu.cn
Contribution: contributed to the data collection

Rongshao Tan: tanrongshao@126.com
Contribution: contributed to the conceptualization of the study, and revised the manuscript critically for important intellectual content.

Corresponding Author: Rong-shao Tan, Guangzhou Institute of Disease-Oriented Nutritional Research, Guangzhou Red Cross Hospital. No.396 of Tongfuzhong Road, Guangzhou, Guangdong, P. R. of China, 510220. Tel: +86-20-61883499. Email: tanrongshao@126.com; Danhua Liang, Department of Nutrition, Shunde Hospital, Southern Medical University, The First People's Hospital of Shunde Foshan, No. 1 Jiazi Road, Lunjiao, Shunde District, Foshan City, Guangdong Province, China, 528308. Tel: Email: 894940278@qq.com

ABSTRACT

Background and Objectives: Protein-energy wasting (PEW) is common among maintenance hemodialysis (MHD) patients and is strongly associated with mortality and adverse outcomes. This study aimed to assess the effects of low-protein energy supplements on the nutritional status of MHD patients with PEW. **Methods and Study Design:** We conducted a prospective randomized controlled trial in 68 MHD patients suffering from PEW. Patients randomized to the intervention group received dietary counseling along with daily low-protein supplements containing 212 kcal of energy and 2.4 g of protein every day for 3 months. The control group received dietary counseling only. Dietary data, nutritional assessments, anthropometric measurements, bioelectrical impedance analysis and blood analysis were collected at baseline and after three months from both groups. **Results:** Fifty-nine MHD patients completed the study. Patients in the intervention group showed an increase in energy intakes ($p < 0.001$). A significant decrease in the Malnutrition Inflammation Score (MIS) ($p < 0.001$) and Nutrition Risk Screening 2002 ($p < 0.001$) were found in the intervention group compared with the control group. Moreover, significant improvements in mid-upper arm circumference ($p < 0.001$), mid-arm muscle circumference ($p < 0.001$), albumin ($p = 0.003$), and prealbumin ($p = 0.033$) were observed in the intervention group compared with the control group. **Conclusions:** The combination of oral low-protein supplements and dietary counseling for three months was more effective than dietary counseling alone in terms of improving the nutritional status of MHD patients with PEW.

Key Words: hemodialysis, low-protein supplements, protein-energy wasting, nutritional status, malnutrition inflammation score

INTRODUCTION

Protein-energy wasting (PEW) is a widespread problem in maintenance hemodialysis (MHD) patients, with incidences ranging from 18% to 75%.[1] It is a state of impaired catabolism resulting from metabolic and nutritional disturbances in chronic kidney disease (CKD) and is characterized by the depletion of body proteins and energy reserves.[2] Several factors contribute to PEW among MHD patients, including insufficient clearance of uremic toxins, inflammation, inadequate protein intake, comorbidities, inadequate physical activity, nutritional losses in dialysate, and endocrine and metabolic disorders.[3, 4] Numerous studies have demonstrated the association of PEW with an elevated risk of morbidity and mortality,

as well as a diminished quality of life.[5] Therefore, timely implementation of nutritional interventions is crucial in the management of MHD patients.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines in 2000 recommended a caloric intake of 35 kcal/kg/day and a dietary protein intake (DPI) of 1.2 g/kg/day for MHD patients.[6] However, many patients fail to meet these recommendations due to factors such as anorexia, dietary restrictions, and socioeconomic limitations.[7] Chen et al. proposed that improvements in dialysis technology and treatment strategies for metabolic disorders and complications may lead to a decrease in the daily protein intake requirement.[8] Moreover, recent research has indicated that DPI of 0.7-0.9 g/kg/day has been sufficient to maintain good nutritional status for hemodialysis patients.[9, 10] Therefore, the latest KDOQI guidelines in 2020 slightly reduced the protein intake and recommend the DPI of 1.0~1.2 g/kg/day in MHD patients.[11] Even though some high protein-containing supplements were found to improve the nutritional status of malnourished MHD patients.[12-14] Increased protein intake can result in higher blood phosphorus levels, which independently increase the risk of mortality in MHD patients.[15] Additionally, higher DPI can exacerbate metabolic acidosis in MHD patients due to increased acidic products produced by protein metabolism. Furthermore, sufficient energy intake played a pivotal role in sparing protein.[16] It can be seen that appropriately adjusting the protein intake of maintenance hemodialysis patients can also maintain their good nutritional status and reduce side effects from excessive protein intake.

While renal-specific oral low-protein nutritional supplements can overcome the problems of energy deficiency and phosphorus overload in MHD patients. Currently, this formulation is commonly used in CKD patients not receiving dialysis, the efficacy of renal specific low-protein calorie oral supplements on MHD patients with PEW remains unexplored. Therefore, in this study, we aimed to investigate the effects of low-protein energy supplements on the nutritional status of MHD patients with PEW.

MATERIALS AND METHODS

Study design and patients

This was a prospective, randomized, controlled, single center clinical study conducted from October 2022 to September 2023. The participants were recruited from the hemodialysis center in Shunde Hospital of Southern Medical University. This study was approved by the Ethics Committee of Shunde Hospital of Southern Medical University (Approval No. KYLS20220775). Informed consent was obtained from all participants prior to their inclusion

in the study. The trial was registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn, ChiCTR2400081663). This trial was conducted in compliance with the principles of the Declaration of Helsinki. The inclusion criteria were patients aged 18 to 80 who were on regular hemodialysis (three times per week for 4 hours each session) for over 3 months, with a Malnutrition Inflammation Score (MIS) ≥ 8 and without nutritional supplements in the last 3 months. The exclusion criteria were patients who required renal transplantation, had experienced trauma, surgery, a peptic ulcer, or a serious infection within the previous 3 months, needed elective surgery, had a confirmed diagnosis of malignancy, or had pacemakers installed.

Intervention protocol

Patients meeting the inclusion criteria were randomized into either the intervention or the control group using a SPSS software-generated randomization table with the permuted block method (block sizes of 4). During the study, all participants received dietary counseling from dietitians. Participants in the intervention group were treated with the oral low-protein supplements dedicated for MHD patients at a daily dosage of 50 g for 3 months. The nutritional content of the supplement are wheat starch, maltodextrin, refined vegetable oil, concentrated whey protein, carrot powder, milk powder, whole egg powder, polydextrose, oligofructose, a vitamin blend and a mineral blend. Each serving (50 g) of the oral nutritional supplements contains 212 kcal of energy, 2.4 g of protein, 5.5 g of lipids, and 37.4 g of carbohydrates, with a reduced content of phosphorus and potassium. Participants visited the hemodialysis units three times a week, where they were provided with 14 servings of the oral nutritional supplements every two weeks.

Study outcomes

MIS is commonly used as a diagnostic tool for PEW. Therefore, the primary outcome was MIS in this study. The secondary outcomes included NRS2002, serum albumin, BMI, serum prealbumin and phosphorus. Other composite nutritional indicators, including laboratory measurements, anthropometric measurements and dietary intake, were also collected. These outcome measurements were assessed at the baseline and at the end of the trial.

Dietary intake

Dietary intake was assessed using three 24-hour diet recalls questionnaires through face-to-face interviews for three days (one dialysis day and two non-dialysis days). The energy intake

of all food and drink items was sourced using a computer aided dietary software (Zhending, Shanghai, China; software version 2.0), in which nutrient models were according to the Chinese Food Composition Table came from the Chinese Center for Disease Control and Prevention in 2018.

Evaluation of nutritional status

The NRS2002 and MIS were utilized as nutritional screening and assessment tools respectively at the baseline and at the third month of the study. The NRS2002 scoring system entails the summation of three component scores, resulting in a total score ranging from 0 to 7. A total NRS2002 score ≥ 3 indicated patients were at nutritional risk.[17] The MIS comprises 10 components, each graded on a severity scale from 0 (normal) to 3 (severely abnormal). The total MIS score ranges from 0 (normal) to 30 (severely malnourished); a higher score reflects a more severe degree of malnutrition and inflammation.[18] Patients with MIS ≥ 8 were diagnosed with PEW.[19]

Laboratory parameters

Blood samples were collected from each participant following a fasting period before the hemodiaysis session and sent for biochemical examination. The serum biochemical parameters [creatinine (Cr), blood urea nitrogen (BUN), prealbumin (PA), albumin (ALB), total cholesterol (TCHOL), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin (Hb), triglyceride, C-reactive protein (CRP), ferritin, total iron binding capacity (TIBC), calcium, phosphorus, sodium, potassium and intact parathyroid hormone (PTH),] were analyzed using a AU5800 automatic biochemical analyzer.

Anthropometrics

The MHD patients had their height and dry weight (post-dialysis weight) measured using electronic column scales (SECA 206, Seca, Germany). Body mass index (BMI) was calculated as weight (kg) / height (m2). Handgrip strength (HGS) was measured using the Xiangshan Electronic Hand Dynamometer (Xiangshan, Zhongshan Camry Electronic Co., Ltd., China). Mid-arm circumference (MAC) was measured with a flexible, non-stretchable measuring tape, while the triceps skinfold (TSF) was measured by the Harpenden skinfold caliper on the non-fistula arm for hemodialysis patients. The mid-arm muscle circumference

(MAMC) was calculated by the following formula: MAMC (cm) = MAC (cm)- π × TSF (mm).

Bioelectrical impedance analysis measurement

The InBody 270 (Biospace, Seoul, Korea) body composition analyzer, a multifrequency BIA device, was used to estimate body composition. The BIA measurement of dialysis patients was conducted 20-30 min after a hemodialysis session with the standardized procedures. BIA-derived fat mass (FM), fat-free mass (FFM), percent body fat (BF%), skeletal muscle mass (SMM), and skeletal muscle mass Index (SMI) values were recorded.

Statistical analysis

The sample size calculation was performed using PASS 15.0.5 software (NCSS, LLC, Kaysville, Utah, USA) based on the results from a previous trial that demonstrated a 2.1 decrease in MIS due to oral nutritional supplementation. In this study, we used a mean difference in MIS of 2.1, with a standard deviation (SD) of 2.7, a type 1 error rate of 5%, and 80% power. Thus, the minimum required sample size was 27 patients in each group. Assuming a drop-out rate of 20%, 34 enrolled patients were required in each group.

SPSS version 21.0 (Statistical Package for the Social Sciences, Chicago, IL) was used for statistical analysis. Values displaying a normal distribution were expressed as mean ± SD, while values with a skewed distribution were expressed as medians (first quartile and third quartile). Categorical data were presented as frequencies (percentages). Baseline characteristics of the two groups were compared using the t-test or the Wilcoxon–Mann–Whitney test for continuous data, and the chi-squared test for categorical data. Change was defined as the value at 3 months minus the value at baseline, and the difference in change between the intervention and control groups was compared using the t-test. Statistically significant differences were considered to be $p < 0.05$.

RESULTS

Baseline characteristics

Three hundred fifty-one patients in our HD unit (n = 351) were assessed for eligibility based on the inclusion and exclusion criteria. Of these, 68 patients were included and randomized; however, 9 participants did not complete the study. Thus, 59 participants were included in the data analysis, comprising 30 patients in the control group and 29 patients in the intervention group (Figure 1). There were no significant differences between the groups regarding age,

gender, dialysis duration, etiology of end-stage renal disease (ESRD), and dialysis adequacy at baseline ($p > 0.05$) (Table 1).

Dietary intake

After three months of oral nutritional supplementation, no significant differences were observed between the groups in the changes in intake of protein, fat, phosphate, sodium, calcium, potassium, vitamin B1, vitamin C, and folic acid throughout the study period ($p > 0.05$). However, the intervention group showed an increase in energy and carbohydrate intake ($p < 0.001$) compared to the control group during the trial (Table 2).

Nutritional scores and measurement findings

It was found that the MIS score and the Nutrition Risk Screening 2002 score in the intervention group significantly decreased compared with the control group ($p < 0.001$). Regarding the anthropometric measurements, MAC and MAMC significantly increased in the intervention group compared with the control group ($p < 0.001$). However, no significant differences were observed in the changes in BMI, HGS, TSF, and bioelectrical impedance analysis measurements between the two groups (Table 3).

Laboratory findings

There were significant increases in albumin ($p = 0.003$) and prealbumin ($p = 0.033$) in the intervention group compared with the control group. However, no significant differences were observed in the changes in hemoglobin, triglycerides, ferritin, TIBC, TCHOL, HDL-C, LDL-C, CRP, BUN, creatinine, calcium, phosphorus, sodium, potassium, and PTH between the two groups (Table 4).

DISCUSSION

Protein-energy wasting is frequent in maintenance dialysis and is closely associated with both increased morbidity/mortality risk and worsened quality of life.[1, 20] Oral nutritional supplements are important for MHD patients with PEW, especially when individual dietary counseling is ineffective. In most previous studies, the clinical efficacy of oral supplements, with and without protein, has been examined in MHD patients.[12, 21-25] Though some high protein-containing supplements have been found to improve the nutritional status of MHD patients with PEW.[12, 14] However, high protein intake may lead to increased ingestion of several potentially harmful substances, particularly phosphate.[4, 26] It is widely recognized that

adequate energy intake plays a crucial role in sparing protein.[16] This suggests that properly reducing the protein while increasing the energy content in supplements may overcome those problems. However, the effectiveness of low-protein calorie supplements in the MHD patients is lacking.

According to a study, many hemodialysis patients consume less energy than the recommended intake of 30-35 kcal/kg/day, with observed intakes around 25.3 kcal/kg/day.[27] This necessitates an additional daily intake of approximately 200 kcal/day. Therefore, this randomized controlled study examines the effects of a renal-specific low-protein calorie supplement with 212 kcal in MHD patients. The hypothesis aims to investigate whether MHD patients at risk of malnutrition can maintain adequate nutritional status by taking a daily oral supplement as compared to patients receiving conventional care. The results of this study indicate that after using the oral supplement, the intervention group showed an increase in energy and carbohydrate intake, but there was no significant increase in protein and phosphorus intake. Therefore, patients who adhered to the supplementation showed an improvement in nutritional status (MIS, NRS2002, Alb, Prealbumin, MAC, and MAMC) without an increase in the serum PTH and phosphorus levels.

Experts recommend NRS2002 as a nutritional risk screening tool[17, 28] and MIS as a nutritional assessment tool for MHD patients.[18] The current study found a significantly decreased MIS score and NRS2002 score in the intervention group compared with control, suggesting that the oral low-protein energy supplements had a positive influence on the nutritional status of MHD patients by increasing energy intake. Our finding is consistent with that of a recent study using oral energy nutritional supplements.[24]

Previous studies have demonstrated that the hemodialysis procedure results in a catabolic state with decreases in whole-body protein synthesis and concomitant increases in whole-body and skeletal muscle breakdown.[11, 29] Muscle wasting and diminished muscle strength are related to poor quality of life, frailty, and a higher risk of hospitalization and mortality in CKD patients.[30, 31] Therefore, our focus was on examining changes in indicators of muscle mass, specifically the MAC and MAMC, over the course of the study. In the present study, MAC and MAMC of participants in the intervention group showed greater improvement than those in the control group after three-month trial, indicating that the low-protein energy supplements could alleviate the muscle loss of MHD patients with PEW. These results corroborate the findings reported by Wen.[25] A possible explanation for this might be that the protein-sparing effect of low-protein energy supplementation contributed to shifting this balance to a positive protein anabolic state in MHD patients.[32] Furthermore, we have also

emphasized the importance of routinely including BIA in assessments of the nutritional status of patients with MHD due to its ease of implementation and utility as a nutrition assessment tool.[33] However, in this study, low-protein energy supplementation did not significantly change the BIA indicators in MHD patients after 3 months of treatment. This outcome could potentially be attributed to the relatively short observation period.

Serum albumin and prealbumin concentrations are robust markers of nutrition, but hypoalbuminemia is likely the strongest predictor of hospitalization and mortality among MHD patients.[34] In this study, we found a significant increase in serum albumin and prealbumin concentrations in the intervention group, although the oral nutrition supplementation we used could mainly supply energy with little protein. Consistent with these results, previous studies reported similar conclusions.[24, 35] This indicates that sufficient energy supply can prevent protein from being utilized as calories by replenishing energy, thus achieving a positive nitrogen balance and ameliorating nutritional status.

Hyperphosphatemia is widespread, and alterations in serum phosphorus levels have been related to subsequent disturbances in circulating parathyroid hormone levels and calcium homeostasis.[36] Such disturbances in mineral bone disease may subsequently lead to vascular calcification.[37] Therefore, current clinical practice guidelines recommend that MHD patients consume a low-phosphorus diet in order to mitigate hyperphosphatemia.[38] Furthermore, an added benefit of the present supplement is its exceptionally low phosphate content (90 mg/100 g), in addition to providing 426 kcal energy per 100 g. Consequently, serum phosphate did not increase in the intervention group, which is a significant benefit to patients. In contrast, an equivalent amount of energy from the diet (e.g., rice) would provided an additional 132 mg dietary phosphate. Although controlling hyperphosphataemia by reducing protein intake is no longer recommended,[39] many patients still avoid high-protein foods in order to mitigate the risk of hyperphosphataemia. Therefore, the use of a supplement with a small amount of phosphate content is very safe for patients with advanced CKD, especially those with ESRD.

The limitations of this study should be recognized. Firstly, the sample size was relatively small, and the duration of the study was insufficient for comprehensive observations of malnutrition. Further research will need to identify the effects of low-protein energy supplements on protein-energy wasting (PEW) using a long-term, large-scale approach. Secondly, the lack of medication records for patients could potentially influence the accuracy of serum biochemical measurements. Despite this, we were unable to precisely monitor the daily protein intakes (DPIs) and total energy intakes (TEIs) because the study's design

involved reviewing 3 days of data from the dietary diaries at monthly intervals only, which is a common approach to assess patient compliance. Additionally, this study lacked follow-up information on long-term prognostic indicators such as hospitalization rates, mortality, and quality of life for patients, all of which are influenced by nutritional status.

Conclusion

In conclusion, we found that the provision of low-protein energy supplements containing 212 kcal of energy and 2.4 g of protein per day can induce a significant improvement in MIS, NRS2002, MAC, MAMC, serum albumin and prealbumin levels. It is concluded that low-protein energy supplements could improve the nutritional status of MHD patients with PEW without significantly increase the serum phosphorus levels.

ACKNOWLEDGEMENTS

We thank all participants involved in this project for their contributions. We thank the medical and nursing staff of Shunde Hospital, Southern Medical University for their support of this study.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

This study was supported by the Scientific Research Start Plan of Shunde Hospital, Southern Medical University (SRSP2021003, CRSP2022010), the Foshan Medical Scientific Research Projects (20230826A010561), and the Medical Science and Technology Research Project of Foshan City (2320001006829).

REFERENCES

1. Carrero JJ, Thomas F, Nagy K, Arogundade F, Avesani CM, Chan M, et al. Global Prevalence of Protein-Energy Wasting in Kidney Disease: A Meta-analysis of Contemporary Observational Studies From the International Society of Renal Nutrition and Metabolism. J Ren Nutr. 2018;28:380-92.doi:10.1053/j.jrn.2018.08.006.
2. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevino-Becerra A, Wanner C. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391-8.doi:10.1038/sj.ki.5002585.
3. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the

International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr. 2013;23:77-90.doi:10.1053/j.jrn.2013.01.001.

4. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int. 2013;84:1096-107.doi:10.1038/ki.2013.147.
5. Oliveira EA, Zheng R, Carter CE, Mak RH. Cachexia/Protein energy wasting syndrome in CKD: Causation and treatment. Semin Dial. 2019;32:493-99.doi:10.1111/sdi.12832.
6. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. Am J Kidney Dis. 2000;35:S17-S104.doi:10.1053/ajkd.2000.v35.aajkd03517.
7. Kistler BM, Fitschen PJ, Ikizler TA, Wilund KR. Rethinking the restriction on nutrition during hemodialysis treatment. J Ren Nutr. 2015;25:81-7.doi:10.1053/j.jrn.2014.08.008.
8. Chen J. Nutrition, phosphorus, and keto-analogues in hemodialysis patients: a Chinese perspective. J Ren Nutr. 2013;23:214-7.doi:10.1053/j.jrn.2013.01.020.
9. Fouque D, Pelletier S, Guebre-Egziabher F. Have recommended protein and phosphate intake recently changed in maintenance hemodialysis? J Ren Nutr. 2011;21:35-8.doi:10.1053/j.jrn.2010.10.025.
10. Li HL, Li H, Cao YF, Qi Y, Wang WQ, Liu SQ, et al. Effects of keto acid supplements on Chinese patients receiving maintenance hemodialysis: a prospective, randomized, controlled, single-center clinical study. Chin Med J (Engl). 2020;133:9-16.doi:10.1097/CM9.0000000000000578.
11. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 Update. Am J Kidney Dis. 2020;76:S1-S107.doi:10.1053/j.ajkd.2020.05.006.
12. Sezer S, Bal Z, Tutal E, Uyar ME, Acar NO. Long-term oral nutrition supplementation improves outcomes in malnourished patients with chronic kidney disease on hemodialysis. JPEN J Parenter Enteral Nutr. 2014;38:960-5.doi:10.1177/0148607113517266.
13. Fouque D, McKenzie J, de Mutsert R, Azar R, Teta D, Plauth M, Cano N, Renilon Multicentre Trial Study G. Use of a renal-specific oral supplement by haemodialysis patients with low protein intake does not increase the need for phosphate binders and may prevent a decline in nutritional status and quality of life. Nephrol Dial Transplant. 2008;23:2902-10.doi:10.1093/ndt/gfn131.
14. Scott MK, Shah NA, Vilay AM, Thomas J, 3rd, Kraus MA, Mueller BA. Effects of peridialytic oral supplements on nutritional status and quality of life in chronic hemodialysis patients. J Ren Nutr. 2009;19:145-52.doi:10.1053/j.jrn.2008.08.004.
15. Dhillon-Jhattu S, Sprague SM. Should phosphate management be limited to the KDIGO/ KDOQI guidelines? Semin Dial. 2018;31:377-81.doi:10.1111/sdi.12702.
16. Thomas DD, Istfan NW, Bistrian BR, Apovian CM. Protein sparing therapies in acute illness and obesity: a review of George Blackburn's contributions to nutrition science. Metabolism. 2018;79:83-96.doi:10.1016/j.metabol.2017.11.020.

17. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M, Educational, Clinical Practice Committee ESoP, Enteral N. ESPEN guidelines for nutrition screening 2002. Clin Nutr. 2003;22:415-21.doi:10.1016/s0261-5614(03)00098-0.
18. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2001;38:1251-63.doi:10.1053/ajkd.2001.29222.
19. Avesani CM, Sabatino A, Guerra A, Rodrigues J, Carrero JJ, Rossi GM, Garibotto G, Stenvinkel P, Fiaccadori E, Lindholm B. A Comparative Analysis of Nutritional Assessment Using Global Leadership Initiative on Malnutrition Versus Subjective Global Assessment and Malnutrition Inflammation Score in Maintenance Hemodialysis Patients. J Ren Nutr. 2022;32:476-82.doi:10.1053/j.jrn.2021.06.008.
20. Sabatino A, Regolisti G, Karupaiah T, Sahathevan S, Sadu Singh BK, Khor BH, Salhab N, Karavetian M, Cupisti A, Fiaccadori E. Protein-energy wasting and nutritional supplementation in patients with end-stage renal disease on hemodialysis. Clin Nutr. 2017;36:663-71.doi:10.1016/j.clnu.2016.06.007.
21. Calegari A, Barros EG, Veronese FV, Thome FS. Malnourished patients on hemodialysis improve after receiving a nutritional intervention. J Bras Nefrol. 2011;33:394-401
22. Tomayko EJ, Kistler BM, Fitschen PJ, Wilund KR. Intradialytic protein supplementation reduces inflammation and improves physical function in maintenance hemodialysis patients. J Ren Nutr. 2015;25:276-83.doi:10.1053/j.jrn.2014.10.005.
23. Bolasco P, Caria S, Cupisti A, Secci R, Saverio Dioguardi F. A novel amino acids oral supplementation in hemodialysis patients: a pilot study. Ren Fail. 2011;33:1-5.doi:10.3109/0886022X.2010.536289.
24. Qin A, Tan J, Hu W, Liu Y, Chen L, Tang Y, Qin W. Oral energy supplementation improves nutritional status in hemodialysis patients with protein-energy wasting: A pilot study. Front Pharmacol. 2022;13:839803.doi:10.3389/fphar.2022.839803.
25. Wen L, Tang C, Liu Y, Jiang J, Zou D, Chen W, et al. Effects of oral non-protein calorie supplements on nutritional status among maintenance hemodialysis patients with protein-energy wasting: a multi-center randomized controlled trial. Food Funct. 2022;13:8465-73.doi:10.1039/d1fo03791a.
26. Kovesdy CP, Shinaberger CS, Kalantar-Zadeh K. Epidemiology of dietary nutrient intake in ESRD. Semin Dial. 2010;23:353-8.doi:10.1111/j.1525-139X.2010.00745.x.
27. Liu Y, Xiao X, Qin DP, Tan RS, Zhong XS, Zhou DY, Liu Y, Xiong X, Zheng YY. Comparison of Intradialytic Parenteral Nutrition with Glucose or Amino Acid Mixtures in Maintenance Hemodialysis Patients. Nutrients. 2016;8.doi:10.3390/nu8060220.
28. Tan R, Long J, Fang S, Mai H, Lu W, Liu Y, Wei J, Yan F. Nutritional Risk Screening in patients with chronic kidney disease. Asia Pac J Clin Nutr. 2016;25:249-56.doi:10.6133/apjcn.2016.25.2.24.
29. Carrero JJ, Chmielewski M, Axelsson J, Snaedal S, Heimburger O, Barany P, Suliman ME, Lindholm B, Stenvinkel P, Qureshi AR. Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. Clin Nutr. 2008;27:557-64.doi:10.1016/j.clnu.2008.04.007.

30. Stenvinkel P, Carrero JJ, von Walden F, Ikizler TA, Nader GA. Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. Nephrol Dial Transplant. 2016;31:1070-7.doi:10.1093/ndt/gfv122.
31. Matsuzawa R, Matsunaga A, Wang G, Yamamoto S, Kutsuna T, Ishii A, Abe Y, Yoneki K, Yoshida A, Takahira N. Relationship between lower extremity muscle strength and all-cause mortality in Japanese patients undergoing dialysis. Phys Ther. 2014;94:947-56.doi:10.2522/ptj.20130270.
32. Iapichino G, Gattinoni L, Solca M, Radrizzani D, Zucchetti M, Langer M, Vesconi S. Protein sparing and protein replacement in acutely injured patients during TPN with and without amino acid supply. Intensive Care Med. 1982;8:25-31.doi:10.1007/BF01686850.
33. Raimann JG, Zhu F, Wang J, Thijssen S, Kuhlmann MK, Kotanko P, Levin NW, Kaysen GA. Comparison of fluid volume estimates in chronic hemodialysis patients by bioimpedance, direct isotopic, and dilution methods. Kidney Int. 2014;85:898-908.doi:10.1038/ki.2013.358.
34. Ikizler TA, Cuppari L. The 2020 Updated KDOQI Clinical Practice Guidelines for Nutrition in Chronic Kidney Disease. Blood Purif. 2021;50:667-71.doi:10.1159/000513698.
35. Gharib MS, Nazeih MS, El Said TW. Effect of intradialytic oral nutritional supplementation on nutritional markers in malnourished chronic hemodialysis patients: prospective randomized trial. BMC Nephrol. 2023;24:125.doi:10.1186/s12882-023-03181-7.
36. Silver J, Naveh-Many T. FGF-23 and secondary hyperparathyroidism in chronic kidney disease. Nat Rev Nephrol. 2013;9:641-9.doi:10.1038/nrneph.2013.147.
37. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM. Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000;87:E10-7.doi:10.1161/01.res.87.7.e10.
38. Kidney Disease: Improving Global Outcomes CKDMBDWG. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009:S1-130.doi:10.1038/ki.2009.188.
39. Locatelli F, Cannata-Andia JB, Drueke TB, Horl WH, Fouque D, Heimburger O, Ritz E. Management of disturbances of calcium and phosphate metabolism in chronic renal insufficiency, with emphasis on the control of hyperphosphataemia. Nephrol Dial Transplant. 2002;17:723-31.doi:10.1093/ndt/17.5.723.

Table 1. Characteristics of the participants at the baseline

Parameters	Control group (n =30)	Intervention (n = 29)	$t/\chi^2/Z$	*p*
Age (years)	63.0 ± 12.5	64.6 ± 10.1	0.57	0.574
Male, n (%)	16 (53.3)	17 (58.6)	0.17	0.683
Dialysis duration (months)	29 (14.5, 56.5)	46 (19.0, 74.5)	-1.15	0.250
Primary diseases, n (%)			5.18	0.159
Chronic glomerulonephritis	10 (33.3)	6 (20.7)		
Diabetic nephropathy	8 (26.7)	15 (51.7)		
Unknown causes	9 (30.0)	4 (13.8)		
Other causes	3 (10.0)	4 (13.8)		
Dialysis adequacy (Kt/V)	1.37 ± 0.20	1.40 ± 0.24	0.51	0.610

Table 2. Nutrient intake of the participants (mean ± SD)

	Control			Intervention			*p*
Parameters	Baseline	3 months	Change	Baseline	3 months	Change	
Energy (kcal/kg BW/d)	28.9 ± 7.44	27.8 ± 5.22	-0.97 ± 3.28	27.5 ± 7.77	31.6 ± 6.90	4.03 ± 1.75	< 0.001
Protein (g/kg BW/d)	1.00 ± 0.29	0.99 ± 0.22	-0.00 ± 0.19	0.99 ± 0.29	1.04 ± 0.28	0.05 ± 0.04	0.207
Energy (kcal/d)	1526 ± 317	1472 ± 332	-40.0 ± 162	1474 ± 381	1591 ± 325	217 ± 96.8	< 0.001
Protein (g/d)	52.8 ± 14.7	52.1 ± 10.9	-0.22 ± 9.76	53.4 ± 15.1	55.6 ± 14.8	2.17 ± 2.20	0.228
Carbohydrate (g/d)	259 ± 53.8	239 ± 52.3	-18.2 ± 27.0	251 ± 64.8	288 ± 84.9	37.3 ± 0.46	< 0.001
Fat (g/d)	30.8 ± 6.87	34.0 ± 7.97	3.54 ± 6.24	28.7 ± 8.60	35.1 ± 9.26	6.46 ± 10.6	0.230
Sodium (mg/d)	1980 ± 530	1954 ± 385	-14.5 ± 213	1819 ± 470	1860 ± 369	40.6 ± 152	0.289
Calcium (mg/d)	450 ± 121	455 ± 96.1	8.50 ± 42.2	414 ± 107	405 ± 112	7.31 ± 36.9	0.914
Phosphorus (mg/d)	881 ± 236	864 ± 176	-11.5 ± 88.8	810 ± 210	822 ± 159	11.8 ± 70.0	0.297
Potassium (mg/d)	1602 ± 434	1584 ± 311	-27.5 ± 1715	1489 ± 385	1523 ± 276	34.4 ± 140	0.160
Vitamin B1(mg/d)	0.82 ± 0.22	0.80 ± 0.16	-0.01 ± 0.08	0.75 ± 0.19	0.72 ± 0.14	-0.03 ± 0.07	0.365
Vitamin C (mg/d)	85.5 ± 22.9	83.8 ± 17.0	-1.12 ± 8.67	78.7 ± 20.4	77.2 ± 21.9	1.50 ± 6.55	0.226
Folic acid (mg/d)	216 ± 57.8	212 ± 41.9	-3.00 ± 22.6	199 ± 51.4	200 ± 35.3	1.85 ± 19.7	0.414

Table 3. Nutritional score and measurement findings of the participants (mean ± SD)

Parameters	Control			Intervention			*p*
	Baseline	3 months	Change	Baseline	3 months	Change	
MIS	10.6 ± 2.63	11.3 ± 2.59	0.73 ± 1.12	10.8 ± 2.59	9.60 ± 2.70	-1.17 ± 1.10	< 0.001
NRS2002	3.03 ± 1.01	3.20 ± 1.19	0.17 ± 0.70	3.34 ± 1.01	2.80 ± 1.31	-0.66 ± 0.81	< 0.001
BMI (kg /m^2)	21.2 ± 2.41	21.0 ± 2.73	-0.14 ± 1.49	20.9 ± 2.92	20.6 ± 2.50	0.17 ± 0.81	0.343
HGS (kg)	13.7 ± 7.67	13.8 ± 7.90	0.14 ± 1.63	12.0 ± 4.18	13.0 ± 4.95	1.04 ± 2.44	0.104
MAC (cm)	23.4 ± 2.01	23.3 ± 1.97	-0.11 ± 0.89	23.6 ± 1.76	24.6 ± 2.27	1.00 ± 1.06	< 0.001
TSF (mm)	8.92 ± 5.21	8.57 ± 4.90	-0.36 ± 0.69	8.74 ± 4.01	9.50 ± 4.23	0.76 ± 3.28	0.078
MAMC (cm)	20.6 ± 1.81	20.6 ± 1.84	0.00 ± 0.85	20.9 ± 1.27	21.6 ± 1.73	0.76 ± 3.28	< 0.001
FM (kg)	11.8 ± 6.44	14.9 ± 8.04	3.18 ± 8.86	14.6 ± 19.8	11.1 ± 4.07	1.12 ± 3.83	0.415
FFM (kg)	42.4±9.50	39.2±7.43	-3.06 ± 9.17	40.1±10.7	41.5±6.71	0.01 ± 7.74	0.294
BF (%)	21.8±11.5	26.9±11.5	5.25 ± 13.5	20.1±8.84	21.0±7.04	2.13 ± 7.99	0.421
SMM (kg)	22.9±5.49	21.1±4.52	-1.89 ± 5.56	20.1±8.84	22.4±3.99	0.01 ± 4.46	0.277
SMI (kg)	6.56±1.36	6.24±0.99	-0.31 ± 1.41	6.38±0.98	6.57±1.03	0.29 ± 0.72	0.135

MIS, malnutrition inflammation score; NRS2002, nutrition risk screening 2002; BMI, body mass index; HGS, handgrip strength; MAC, mid-arm circumference; TSF, triceps skinfold; MAMC, mid-arm muscle circumference; FM, fat mass; FFM, fat-free mass; BF (%), percent body fat; SMM, skeletal muscle mass; and SMI ,skeletal muscle mass Index

Table 4. Serum biochemical measurements of the participants (mean ± SD)

	Control			Intervention			*p*
Parameters	Baseline	3 months	Change	Baseline	3 months	Change	
Albumin (g /L)	36.6 ± 3.66	34.1± 3.53	-2.27 ± 3.34	36.4 ± 2.67	36.7 ± 2.68	0.43 ± 2.75	< 0.001
Prealbumin (mg/L)	271 ± 82.0	248 ± 77.3	-28.9 ± 54.0	251 ± 76.1	255 ± 73.0	4.43 ± 45.3	0.033
Hemoglobin (g/L)	98.7 ± 21.7	101 ± 23.1	2.58 ± 26.5	97.5 ± 16.6	106 ± 21.7	8.86 ± 18.5	0.314
Triglyceride (mmol /L)	1.31 ± 0.74	1.28 ± 0.81	-0.04 ± 0.87	1.10 ± 0.70	1.13 ± 0.53	0.02 ± 0.63	0.792
Ferritin (µg/L)	46.1 ± 8.94	40.6 ± 9.18	29.3 ± 121.5	-4.66 ± 7.49	42.3 ± 9.97	-1.34 ± 7.02	0.656
TIBC (µmol/ L)	46.1 ± 8 .93	39.8 ± 9.29	-1.34 ± 7.02	42.7 ± 10.8	43.0 ± 11.1	-4.66 ± 7.49	0.112
TCHOL (mmol /L)	3.49 ± 1.21	3.07 ± 0.89	-0.41 ± 1.01	3.52 ± 0.97	3.39 ± 0.90	-0.17 ± 0.60	0.283
HDL-C (mmol /L)	1.07 ± 0.35	0.89 ± 0.39	-0.15 ± 0.38	1.23 ± 0.34	1.16 ± 0.34	-0.08 ± 0.21	0.359
LDL-C (mmol /L)	2.13 ± 0.84	1.89 ± 0.56	-0.24 ± 0.73	2.03 ± 0.71	2.04 ± 0.58	-0.04 ± 0.60	0.279
CRP (mg/L)	6.57 ± 15.7	7.48 ± 9.19	1.05 ± 16.8	6.93 ± 8.93	5.37 ± 3.79	-1.64 ± 9.44	0.473
BUN (mmol/ L)	24.8 ± 7.26	23.8 ± 7.33	-1.23 ± 8.94	27,5 ± 13.0	24.3 ± 8.66	-3.89 ± 12.7	0.385
Creatinine (µmo l/L)	923 ± 387	926 ± 346	-16.3 ± 228	855 ± 233	896 ± 273	28.9 ± 148	0.394
Calcium (mmol/L)	2.07 ± 0.21	2.00 ± 0.21	-0.07 ± 0.26	2.12 ± 0.19	2.12 ± 0.24	0.01 ± 0.24	0.308
Phosphorus (mmol/L)	1.70 ± 0.41	1.67 ± 0.35	-0.05 ± 0.38	1.78 ± 0.49	1.78 ± 0.37	-0.03 ± 0.53	0.854
Sodium (mmol/L)	137 ± 3.05	136 ± 2.93	-0.04 ± 3.04	137 ± 3.71	137 ± 3.22	-0.44 ± 2.32	0.586
Potassium (mmol/L)	4.72 ± 0.76	4.61 ± 0.86	0.04 ± 1.08	4.76 ± 0.92	4.85 ± 0.93	-0.19 ± 1.03	0.423
PTH (pg/mL)	377 ± 358	306 ± 340	-45.7 ± 303	624 ± 727	348 ± 261	-303 ± 650	0.066

TIBC,total iron binding capacity; TCHOL, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; BUN, blood urea nitrogen; Na, Natrium; K, potassium; and PTH, parathyroid hormone

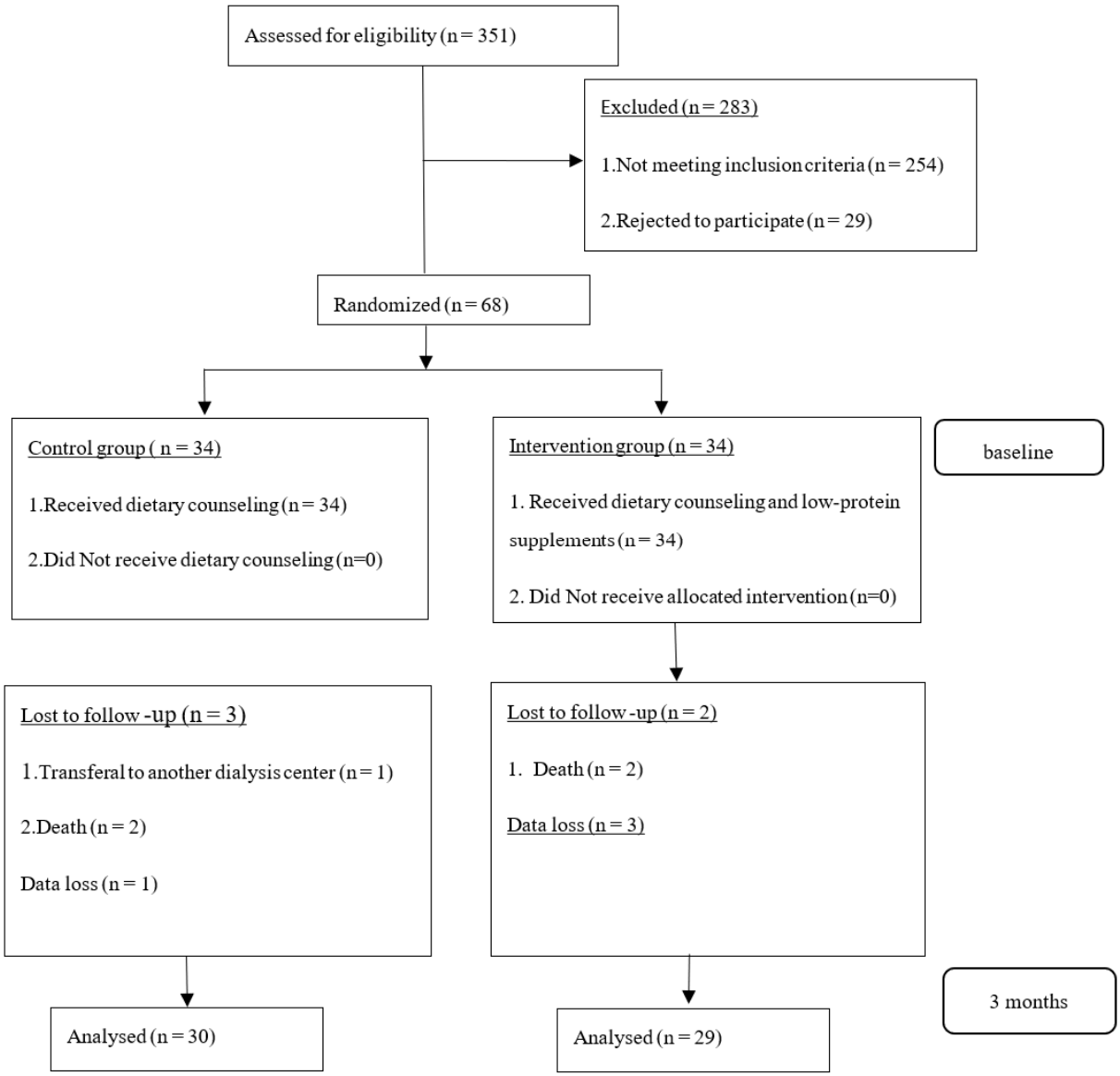

Figure 1. Flow chart of patient enrollment