ORIGINAL RESEARCH

High-Energy Low-Protein Formula Plus Low-Protein Diet Improves Subjective Global Assessment-Defined Nutritional Status in Nondialysis Chronic Kidney Disease: An Open-Label Randomized Trial

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Objective: Protein-energy wasting is common in chronic kidney disease (CKD) and maintaining adequate energy intake while counseling patients toward a low-protein diet remains challenging. We evaluated whether adding a kidney-specific, high-energy low-protein formula containing free amino acids, dietary fiber, vitamins, and minerals to dietitian-led counseling improved nutritional status in nondialysis CKD stages 3-5.

Methods: In this 6-month, single-center, open-label, largely randomized trial analyzed according to the as-treated principle, all participants received counseling toward protein intake of 0.6-0.8 g/kg ideal body weight/day and energy intake of 25-35 kcal/kg ideal body weight/day. The intervention group (n = 48) received 2 daily sachets of the study formula; controls (n = 48) received counseling alone. The primary outcome was improvement in subjective global assessment (SGA) score at 6 months, defined as an increase of at least 1 point.

Results: The intervention group had a higher proportion of participants with SGA improvement than controls (47.9% vs. 25.0%; $P = .020$; odds ratio, 2.76; 95% confidence interval, 1.16-6.55). Excluding within-category transitions from SGA score 6 to 7 yielded a similar result (44.4% vs. 25.0%; $P = .049$). The intervention effect was greatest in participants with baseline body mass index <23 kg/m^2. Nutritional profiles favored the intervention, and the between-group difference in estimated glomerular filtration rate decline slope was not significant.

Conclusions: In nondialysis CKD stages 3-5, adding a kidney-specific, high-energy low-protein formula to counseling toward low-protein diet targets was associated with improved SGA-defined nutritional status without evidence of accelerated estimated glomerular filtration rate decline over 6 months.

Keywords: chronic kidney disease; protein-energy wasting; high-energy low-protein formula; low-protein diet; subjective global assessment

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Introduction

PROTEIN-ENERGY WASTING (PEW) is a pathological state common in nondialysis chronic kidney disease (CKD), characterized by the systemic depletion of protein and energy stores and driven by metabolic abnormalities such as uremic anorexia and chronic inflammation.[1] With a prevalence ranging from 11% to 54% in nondialysis CKD, PEW is strongly associated with adverse outcomes, including accelerated kidney failure, increased hospitalization, and mortality.[2,3] Consequently, global guidelines, including those from

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Support: This research was supported by a research grant from Morris Enterprise CO., LTD (Taipei, Taiwan).

Financial Disclosure: The authors declare that they have no relevant financial interests.

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1051-2276

https://doi.org/10.1053/j.jrn.2026.06.009

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the International Society of Renal Nutrition and Metabolism (ISRNM), the Kidney Disease Outcomes Quality Initiative (KDOQI), and Kidney Disease: Improving Global Outcomes (KDIGO), emphasize a multidimensional diagnostic framework, integrating the subjective global assessment (SGA) with objective functional and body composition metrics, such as handgrip strength (HGS), mid-arm muscle circumference (MAMC), and bioelectrical impedance analysis (BIA).[4–9]

Regarding dietary management, patients with CKD stages 3-5 are generally advised to restrict protein intake (approximately 0.8 g/kg/day) while maintaining sufficient energy intake (25-35 kcal/kg/day) to prevent catabolism.[4,7] However, achieving this balance is clinically challenging; a low-protein diet (LPD) without adequate caloric compensation may contribute to insufficient nonprotein energy intake and increase the risk of PEW in some patients. This dilemma is particularly significant in Asian populations, who typically present with a lower body mass index (BMI) and lower baseline caloric consumption compared to Western counterparts.[3,10] In Taiwan, local studies indicate that predialysis patients often experience caloric insufficiency and imbalanced macronutrient distribution when attempting to adhere to LPDs.[11–13]

To assist patients in achieving energy targets, high-energy low-protein formulas (HE-LPFs) serve as kidney-specific supplements. Although HE-LPFs have shown promise in improving dietary adherence, previous local studies were often limited by small sample sizes, short durations, and incomplete assessments of PEW domains.[14–17] Specifically, few studies have simultaneously evaluated changes in SGA, anthropometrics, and renal function. Therefore, this 6-month randomized controlled trial aimed to comprehensively evaluate the effects of HE-LPFs on nutritional status, body composition, and renal function in Taiwanese patients with CKD stages 3-5. Furthermore, we examined whether baseline characteristics, particularly BMI, modified the intervention effect to provide evidence-based strategies for this vulnerable population.

Methods

Study Design and Participants

This single-center, prospective, open-label, largely randomized controlled trial was conducted at a tertiary CKD clinic. We consecutively screened 104 adults aged 20-80 years. Eligible participants had CKD stages 3-5[4,18] under regular follow-up, preserved oral intake, and ongoing or clinically indicated LPD therapy. Exclusion criteria included acute kidney injury, hospitalization within 3 months, active malignancy receiving therapy, nasogastric tube feeding, major surgery, liver cirrhosis, autoimmune diseases, organ transplantation, and poor adherence to dietary intervention, as evaluated by the dietitian. The study was approved by the institutional review board of the participating hospital (IRB No. B-ER-111-016), and all participants provided written informed consent.

Group Allocation and Intervention

Allocation and Analysis Principles

Participants were initially randomized 1:1 using a computer-generated sequence. Because long-term adherence to nutritional intervention was a major practical concern, pre-intervention reassignment was allowed after consultation for participants with strong treatment preferences. The study was therefore open-label and analyzed according to the as-treated principle, with participants classified according to the intervention actually received rather than the initial assignment (Fig. 1). Accordingly, the design is described as largely randomized rather than fully randomized.

Standard of Care

Participants in both groups received identical medical care and individualized nutritional counseling from a single experienced renal dietitian based on the 2020 KDOQI guideline. Counseling was directed toward a protein intake target of 0.6-0.8 g/kg ideal body weight (IBW)/day and energy intake of 25-35 kcal/kg IBW/day.[4,7] Routine visits included standardized nutritional assessment, exercise recommendations, and review of 24-hour dietary recalls and food records.[19]

Intervention Group: Kidney-Specific High-Energy, Low-Protein Oral Formula

In addition to standard care, a kidney-specific oral formula (Noah Protein minus-protein; Jetton Biochemistry Co., Ltd. (New Taipei City, Taiwan), is consumed between meals. The daily supplementation provided approximately 450 kcal, 0.8 g protein, 79 g carbohydrate, 15.4 g fat, and 4 g dietary fiber, together with arginine 300 mg, glutamine 200 mg, taurine 38 mg, methionine 24 mg, and multiple vitamins, macrominerals, and trace elements. The formula was designed to provide high energy density with low nitrogen and relatively low electrolyte load (Table S1). Adherence was assessed by counting returned sachets at each follow-up visit.

Control Group

Control participants received the same dietitian-led counseling and routine follow-up, but no placebo supplement. They continued their habitual diet under counseling alone without addition of the study formula.

Study Procedures and Assessments

Assessments were performed at baseline (M0), month 3 (M3), and month 6 (M6). To reduce interobserver variability, the same dietitian and research nurse conducted all standardized clinical and nutritional evaluations. Routine measurements included systolic and diastolic blood pressure, height, body weight (BW), and BMI.

Nutritional Assessment

A trained dietitian assessed nutritional status using the 7-point SGA, categorized as SGA-A (scores 6-7), SGA-B (3-5), and SGA-C (1-2).[4] Dietary intake was estimated from 24-hour dietary recalls.[19] Gastrointestinal symptoms were

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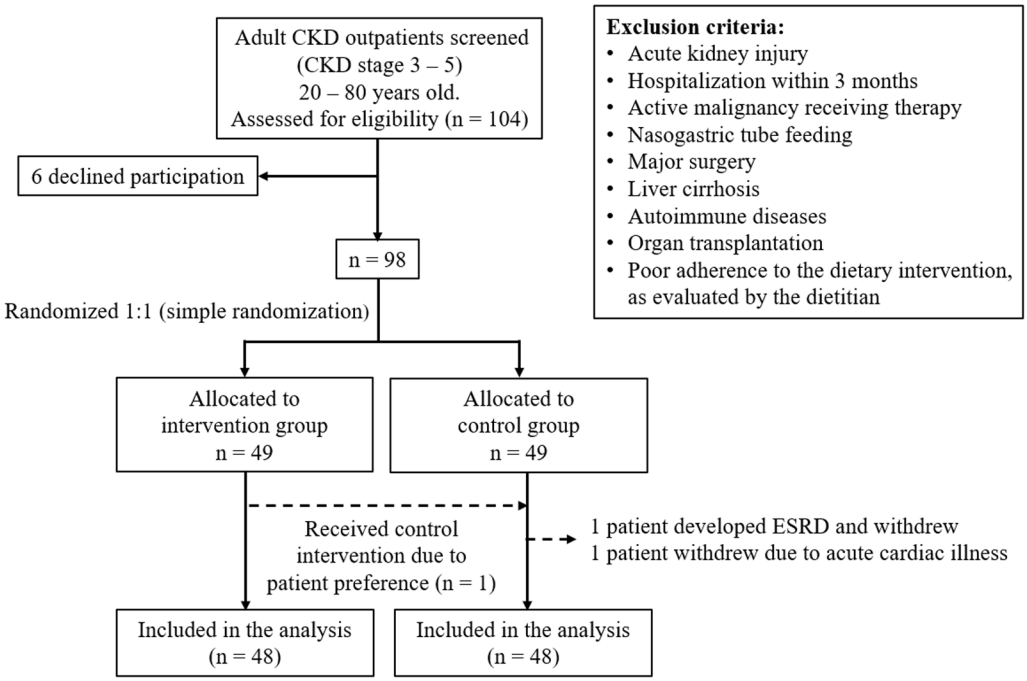


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of participant recruitment, randomization, treatment allocation, and follow-up. A total of 104 adults with CKD stages 3-5 were screened at a tertiary medical center outpatient clinic; 6 declined participation, leaving 98 patients who were randomized 1:1 to the HE-LPF intervention (n = 49) or standard-diet control (n = 49). After randomization, 1 patient assigned to the intervention arm crossed over to the control arm because of treatment preference, and 2 control patients discontinued follow-up (1 progressed to end-stage renal disease and initiated dialysis; 1 was hospitalized for an acute cardiac illness). The final as-treated analysis population comprised 96 participants who completed all three study visits (intervention, n = 48; control, n = 48). CKD, chronic kidney disease; HE-LPFs, high-energy low-protein formulas.

assessed using a structured questionnaire (Table S2). For the "difficulty eating normal portions" item, scores ranged from 0 to 3, with higher scores indicating greater difficulty with oral intake. Because urinary nitrogen excretion was not measured, dietary protein intake was not objectively validated biochemically.

Anthropometric and Strength Measurements

Anthropometric parameters included mid-arm circumference and triceps skinfold thickness (TSF), from which MAMC was calculated using standard equations.[5,7,20] Functional status was assessed by dominant HGS using a dynamometer and pinch strength, using the maximal value from three trials for analysis.[21–24]

Body Composition Analysis

Body composition was assessed via BIA to estimate body fat, lean body mass, and water distribution[5,7]; device specifications and measurement conditions are provided in the supplementary methods.

Laboratory Investigations

Laboratory investigation included hemoglobin, serum albumin, liver function tests, high-sensitivity C-reactive protein (hs-CRP), and serum lipid profiles. Renal function was assessed using the urine protein-to-creatinine ratio and estimated glomerular filtration rate (eGFR), calculated using the standardized formula.[18] Additional assay details are provided in the supplementary methods.

Inflammatory and Metabolic Indices

The hs-CRP-to-albumin ratio was defined as hs-CRP (mg/L) divided by serum albumin (g/dL),[25] and the triglyceride–glucose index was calculated as Ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2].[26]

Outcome Definitions

Primary Outcome

The primary outcome was SGA improvement at 6 months, defined as an increase of at least 1 point in the 7-point SGA score from baseline to month 6. Because a transition from score 6 to 7 remains within SGA-A, sensitivity analyses were performed by either excluding 6-7 transitions or classifying them as nonimprovement. In addition, the proportion of participants classified as SGA-A at month 6 was examined as a related categorical nutritional outcome, including within-group comparison at 6 months. Prespecified subgroup analyses used BMI <24 versus ≥ 24 kg/m^2 based on Taiwanese definition of overweight,[27] and BMI <23 versus ≥ 23 kg/m^2, based on ISRNM threshold for PEW risk.[5]

Secondary Outcomes

Secondary outcomes included dietary intake, anthropometric and functional measures, BIA-derived body

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composition, renal function trajectories, biochemical profiles, and safety/tolerability outcomes.[5,7,20-26]

Statistical Analysis

Normality was assessed using the Shapiro-Wilk test. Continuous variables are presented as mean ± SD or median [IQR] and categorical variables as number (%). Between-group comparisons used the independent t-tests or Mann–Whitney U tests, whereas within-group comparisons used the paired t-tests or Wilcoxon signed-rank tests. Categorical comparisons used the chi-square test, Fisher's exact test, or McNemar's test.

The primary outcome was analyzed using risk differences (RDs), relative risks (RRs), and odds ratios (ORs). Effect modification by BMI was assessed using the prespecified cutoff of <24 versus ≥24 kg/m^2 and <23 versus ≥ 23 kg/m^2 with[5,27] stratified analyses performed using the Cochran–Mantel–Haenszel tests and homogeneity assessed by the Breslow-Day test where appropriate. Multivariable logistic regression was used to examine factors associated with SGA improvement at 6 months. Covariates for body-size adjustment were considered with reference to univariate analyses and clinical relevance. Model 1 included age and sex. Baseline BMI was examined in model 2 as a standardized anthropometric index commonly used in clinical practice. Baseline BW, selected with reference to univariate analyses and clinical relevance, was examined in model 3 as an alternative body size adjustment.

Renal outcomes included binary clinical thresholds (eGFR decline >30% and urine protein-to-creatinine ratio reduction >50%)[4,28] and longitudinal trajectories modeled using linear mixed models (LMMs) with group-by-time interaction.

Secondary within-group analyses were considered exploratory, and no formal adjustment for multiple comparisons was applied.

The numbers of participants included in each analysis, along with reasons for dropout and exclusions, are summarized in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Analyses were performed on complete-case data (<5% missingness) using SPSS version 27 (IBM Corp., Armonk, NY, USA), with significance at two-sided $P < .05$.

Statistical data visualization, including the forest plot, was performed using Python in Google Colab. The plotting scripts were initially drafted with assistance from Gemini (Google, Mountain View, CA, USA) and were subsequently verified and manually refined by authors.

Results

Participant Flow and Follow-Up

Of 104 screened patients, 98 were randomized. One participant assigned to the intervention arm requested reassignment to the control arm before initiation of the intervention; therefore, the as-treated baseline population comprised 48 intervention participants and 50 control participants. During follow-up, two control participants withdrew because of end-stage renal disease progression and a cardiovascular event. Ultimately, 96 participants (48 in each group) completed the 6-month follow-up and were included in the final analysis (Fig. 1).

Baseline Characteristics

Baseline demographics, anthropometrics, body composition, and laboratory characteristics are summarized in Table 1. Baseline characteristics were generally similar between groups, although the intervention group was slightly younger (median 65 vs. 68 years; $P = .048$) and had lower baseline BMI (22.8 vs. 25.1 kg/m^2) and hip circumference ($P < .05$) than the control group. Nutritionally, the intervention group had lower baseline energy intake (27.9 vs. 30.5 kcal/kg), lower protein intake per IBW (P/IBW; 0.78 vs. 1.00 g/kg/day; $P < .001$), and a lower proportion of total energy derived from protein (12.3% vs. 13.6% of total energy; $P = .005$), but a higher proportion of total energy derived from carbohydrate (56.9% vs. 53.0%; all $P < .05$). Use of renin–angiotensin–aldosterone system inhibitors was more frequent in the intervention group (52.1% vs. 25.0%; $P = .006$). Baseline gastrointestinal symptoms were similar between groups, and the distribution of kidney disease etiologies is summarized in Table S3.

Primary Outcome: Changes in Subjective Global Assessment

Unadjusted Analysis

From baseline to month 6, the intervention group showed a significant within-group increase in the proportion of participants classified as SGA-A (54.2%-79.2%, $P = .017$), whereas the corresponding change in the control group was not significant (60.4%-68.8%) (Table 2). Median SGA score also improved in the intervention group but not in the control group (Table S4). However, the absolute proportion of participants classified as SGA-A at month 6 did not differ significantly between groups. In contrast, when nutritional improvement was defined as an increase of at least 1 point in SGA score, a significantly greater proportion of participants in the intervention group met this criterion than in the control group (47.9% vs. 25.0%; $P = .020$). The corresponding RD, risk ratio, and OR were 22.9% (95% CI, 4.2%-41.6%), 1.92 (95% CI, 1.08-3.40), and 2.76 (95% confidence interval [CI], 1.16-6.55), respectively (Table 3).

Sensitivity Analyses

Because scores of 6 and 7 both fall within the SGA-A category, additional sensitivity analyses were performed to examine the robustness of the primary outcome. When participants with within-category transitions from score 6 to 7 were excluded, the intervention group remained more likely to show SGA improvement than the control group (44.4% vs. 25.0%; RD, 19.4%; 95% CI,

Table 1. Baseline Clinical, Anthropometric, Nutritional, Body Composition, Laboratory and Treatment Characteristics of the Study Participants

Characteristic	Control Group (n = 48)	Intervention Group (n = 48)	*P* Value
Clinical characteristics			
Age, years	68 (64-75)	65 (57-71)	.048
Male sex	26 (54.2)	22 (45.8)	.414
Anthropometric measures			
BMI, kg/m^2	25.1 (22.6-26.9)	22.8 (20.7-25.1)	.008
HC, cm	94.7 ± 8.4	90.6 ± 7.9	.018
TSF, mm	14.8 (12.0-20.0)	16.5 (12.8-21.7)	.595
MAMC, cm	20.2 (19.3-22.6)	19.1 (17.4-22.4)	.100
HGS, kg	24.5 (18.3-34.5)	22.2 (17.7-31.7)	.461
PS, kg	7.3 ± 2.1	7.2 ± 2.3	.809
Nutritional assessment			
E/IBW, kcal/kg	30.5 (26.9-31.9)	27.9 (25.0-29.2)	.008
Carbohydrate intake, % of total energy	53.0 ± 6.5	56.9 ± 6.4	.018
Protein intake, % of total energy	13.6 ± 2.1	12.3 ± 2.5	.005
P/IBW, g/kg	1.00 (0.89-1.22)	0.78 (0.68-1.01)	<.001
Fat intake, % of total energy	32.8 ± 5.0	30.9 ± 4.8	.060
SGA score	6.0 (5.0-6.0)	6.0 (4.3-6.0)	.251
SGA–A	29 (60.4)	26 (54.2)	.540
SGA–B	19 (39.6)	22 (45.8)	
SGA–C	0 (0)	0 (0)	
Body composition (BIA)			
Fat mass, kg	15.4 ± 5.2	13.8 ± 4.0	.157
LBM, kg	46.7 (39.3-53.7)	41.4 (36.5-51.7)	.367
Water/BW, %	58.1 ± 6.5	57.7 ± 4.8	.533
Laboratory examination			
Serum urea nitrogen, mg/dL	35.0 (27.3-42.5)	31.0 (26.5-46.0)	.924
Serum creatinine, mg/dL	2.00 (1.65-2.89)	2.15 (1.70-3.26)	.692
eGFR, mL/min/1.73 m^2	27.0 (18.3-37.0)	28.0 (17.5-37.0)	.540
UPCR, mg/g	554.0 (108.0-1440.0)	431.5 (171.5-1386.0)	.613
Serum albumin, g/dL	4.42 ± 0.36	4.39 ± 0.36	.631
hsCRP, mg/L	0.98 (0.38-2.89)	1.10 (0.44-3.86)	.702
hsCAR	0.27 (0.08-0.75)	0.24 (0.11-0.91)	.668
HbA1c, %	6.0 (5.8-6.2)	6.2 (5.7-6.6)	.304
Total cholesterol, mg/dL	157.5 (140.5-185.5)	156.5 (142.0-173.5)	.690
Triglycerides, mg/dL	114.0 (79.0-155.0)	105.5 (81.5-143.5)	.350
LDL-C, mg/dL	85.5 (68.5-104.5)	89.5 (71.0-110.0)	.598
HDL-C, mg/dL	49.0 (39.5-66.5)	50.0 (43.5-62.5)	.944
TyG	8.80 (8.39-9.10)	8.64 (8.35-8.90)	.422
Treatment during trial			
RAAS blockade	12 (25.0)	25 (52.1)	.006
Lipid-lowering agents	27 (56.3)	24 (50.0)	.784
Ketoanalogues	5 (10.4)	5 (10.4)	1.000

BIA, bioelectrical impedance analysis; BMI, body mass index; E/IBW, energy intake to ideal body weight ratio; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HC, hip circumference; HDL-C, high-density lipoprotein cholesterol; HGS, handgrip strength; hsCAR, high-sensitivity C-reactive protein-to-albumin ratio; hsCRP, high-sensitivity C-reactive protein; LBM, lean body mass; LDL-C, low-density lipoprotein cholesterol; MAMC, mid-arm muscle circumference; P/IBW, protein intake to ideal body weight ratio; PS, pinch strength; RAAS, renin–angiotensin–aldosterone system; SGA, subjective global assessment; SGA-A, subjective global assessment grade A (score 6-7); SGA-B, subjective global assessment grade B (score 3-5); SGA-C, subjective global assessment grade C (score 1-2); TSF, triceps skinfold thickness; TyG, triglyceride–glucose index; UPCR, urine protein-to-creatinine ratio.

Data are presented as means ± SDs (normally distributed data), medians (interquartile ranges) (non-normally distributed data), or numbers (percentages).

0.00-0.38; RR, 1.78; 95% CI, 0.99-3.20; OR, 2.40; 95% CI, 1.00-5.78; $P = .049$). Similar directionality was observed when transitions from score 6 to 7 were classified as nonimprovement (41.7% vs. 25.0%; OR, 2.14; 95% CI, 0.90-5.11; $P = .083$) (Table S6).

Subgroup Analysis by BMI and Heterogeneity Testing

Prespecified subgroup analyses were performed using two BMI thresholds: BMI <24 vs. ≥24 kg/m^2, based on Taiwanese definition of overweight,[27] and <23 vs.

Table 2. Within-Group Changes From Baseline (M0) to 6 months (M6) in Anthropometric, Nutritional, Body Composition, and Laboratory Parameters in the Control and Intervention Groups

	Control Group (n = 48)			Intervention Group (n = 48)			
Characteristic	M0	M6	*P* Value	Characteristic	M0	M6	*P* Value
Anthropometric Measures							
BMI, kg/m^2	25.1 ± 3.4	25.4 ± 3.5	.026	BMI, kg/m^2	22.8 (20.7-25.1)	23.3 (20.9-25.5)	<.001
MAMC, cm	20.2 (19.3-22.6)	20.6 (19.3-22.1)	.529	MAMC, cm	19.1 (17.4-22.4)	19.4 (17.8-23.2)	.041
HGS, kg	24.5 (18.3-34.5)	28.2 (21.7-37.5)	<.001	HGS, kg	22.2 (17.7-31.7)	26.0 (19.3-36.3)	<.001
Nutritional assessment				Nutritional assessment			
E/IBW, kcal/kg	30.5 (26.9-31.9)	29.0 (25.8-32.9)	.727	E/IBW, kcal/kg	27.7 ± 4.3	30.5 ± 3.7	<.001
CHO intake, % of total energy	53.7 ± 6.5	53.6 ± 5.7	.958	CHO intake, % of total energy	57.3 (52.6-61.3)	61.4 (57.2-63.7)	.004
P/IBW, g/kg	1.00 (0.89-1.22)	0.94 (0.84-1.12)	.317	P/IBW, g/kg	0.78 (0.68-1.01)	0.77 (0.64-0.88)	.033
SGA–A	29 (60.4)	33 (68.8)	.503	SGA–A	26 (54.2)	38 (79.2)	.017
SGA–B	19 (39.6)	15 (31.3)		SGA–B	22 (45.8)	10 (20.8)	
SGA–C	0 (0)	0 (0)		SGA–C	0 (0)	0 (0)	
Body composition				Body composition			
Fat mass, kg	15.4 ± 5.1	16.5 ± 5.6	.016	Fat mass, kg	13.1 (10.5-16.3)	13.7 (11.0-16.8)	.791
LBM, kg	48.0 ± 11.2	47.7 ± 10.5	.441	LBM, kg	45.9 (37.3-52.2)	44.2 (37.2-54.7)	.058
Laboratory examination							
Serum urea nitrogen, mg/dL	35.0 (27.5-42.0)	37.5 (26.5-44.5)	.013	Serum urea nitrogen, mg/dL	31.0 (26.5-46.0)	32.0 (23.0-46.5)	.267
eGFR, mL/min/1.73 m^2	28.3 ± 11.1	26.5 ± 12.3	.012	eGFR, mL/min/1.73 m^2	28.0 (17.5-37.0)	24.0 (15.8-31.5)	<.001
UPCR, mg/g	554.0 (108.0-1440.0)	390.0 (158.0-1333.0)	.541	UPCR, mg/g	431.5 (171.5-1386.0)	454.5 (172.5-1350.5)	.659
LDL-C, mg/dL	85.5 (68.5-104.5)	84.5 (70.0-97.0)	.890	LDL-C, mg/dL	92.7 ± 27.8	83.9 ± 28.8	.029
Serum albumin, g/dL	4.50 (4.20-4.70)	4.30 (4.15-4.50)	.002	Serum albumin, g/dL	4.39 (4.20-4.70)	4.40 (4.20-4.60)	.339

BMI, body mass index; BW, body weight; CHO, carbohydrate; E/IBW, energy intake to ideal body weight ratio; eGFR, estimated glomerular filtration rate; HGS, handgrip strength; LBM, lean body mass; LDL-C, low-density lipoprotein cholesterol; M0, baseline; M6, 6 months; MAMC, mid-arm muscle circumference; P/IBW, protein intake to ideal body weight ratio; SGA-A, Subjective Global Assessment grade A (score 6-7); SGA-B, Subjective Global Assessment grade B (score 3-5); SGA-C, Subjective Global Assessment grade C (score 1-2); UPCR, urine protein-to-creatinine ratio.

Data are presented as means ± SDs (normally distributed data), medians (interquartile ranges) (non-normally distributed data), or numbers (percentages).

Table 3. Effect of Nutritional Intervention on Score-Based Subjective Global Assessment (SGA) Improvement at 6-Month Follow-Up

Outcome	Control (N = 48)	Intervention (N = 48)	RD (95% CI)	RR (95% CI)	OR (95% CI)	*P* Value
Score-based SGA improvement	12 (25.0%)	23 (47.9%)	22.9% (4.2%-41.6%)	1.92 (1.08-3.40)	2.76 (1.16-6.55)	.020

CI, confidence interval; OR, odds ratio; RD, risk difference; RR, relative risk; SGA, subjective global assessment.

SGA improvement was defined as an increase of at least 1 point in the 7-point SGA score. Alternative handling of transitions from score 6 to 7 within SGA-A was examined in sensitivity analyses (Table S6). *P* values were calculated using Pearson's chi-square test.

≥23 kg/m^2, based on ISRNM threshold for increased risk of PEW.[5] Using the 24 kg/m^2 cutoff, no significant heterogeneity was observed (*P* for interaction = .182), although the intervention showed a significant benefit in participants with BMI <24 kg/m^2 (OR, 4.60; 95% CI, 1.23-17.20; *P* = .032). Using the 23 kg/m^2 cutoff, a significant interaction was observed (*P* for interaction = .048). The intervention effect was most pronounced in participants with BMI <23 kg/m^2 (OR, 8.80; 95% CI, 1.58-48.97; *P* = .007), whereas no significant difference was observed in those with BMI ≥23 kg/m^2. These findings suggest that the intervention may be particularly beneficial in patients with lower BMI or high PEW risk (Fig. 2).

Multivariable Logistic Regression Analysis

In model 1, adjusted for age and sex, the intervention remained significantly associated with SGA improvement (adjusted OR, 2.64; 95% CI, 1.09-6.39; *P* = .031). In model 2, adjusted for age, sex, and baseline BMI, the estimated effect size was attenuated but remained directionally consistent (adjusted OR, 2.32; 95% CI, 0.93-5.75; *P* = .070). In model 3, adjusted for age, sex, and baseline BW, the direction of association remained similar (adjusted OR, 2.38; 95% CI, 0.95-5.98; *P* = .066), while lower baseline BW was independently associated with a higher likelihood of SGA improvement (adjusted OR, 0.94 per kg; 95% CI, 0.89-0.99; *P* = .017) (Table 4). In univariate analysis, lower baseline BW, lower BMI, lower energy intake, smaller waist circumference, smaller hip circumference, and lower fat mass were associated with SGA improvement (Table S7).

Secondary Outcomes

Nutritional Status and Dietary Intake

Over 6 months, the intervention group showed a significant increase in estimated energy intake (27.7-30.5 kcal/kg; *P* < .001) and in the proportion of total energy derived from carbohydrate (57.3%-61.4%), together with decreases in the proportion of total energy derived from protein (12.4%-10.2%) and in protein intake per IBW (0.78-0.77 g/kg; all *P* < .05; Table 2). In contrast, the control group showed no significant changes in dietary variables (Table S4). At month 6, compared with the control group, the intervention group had a higher proportion of total

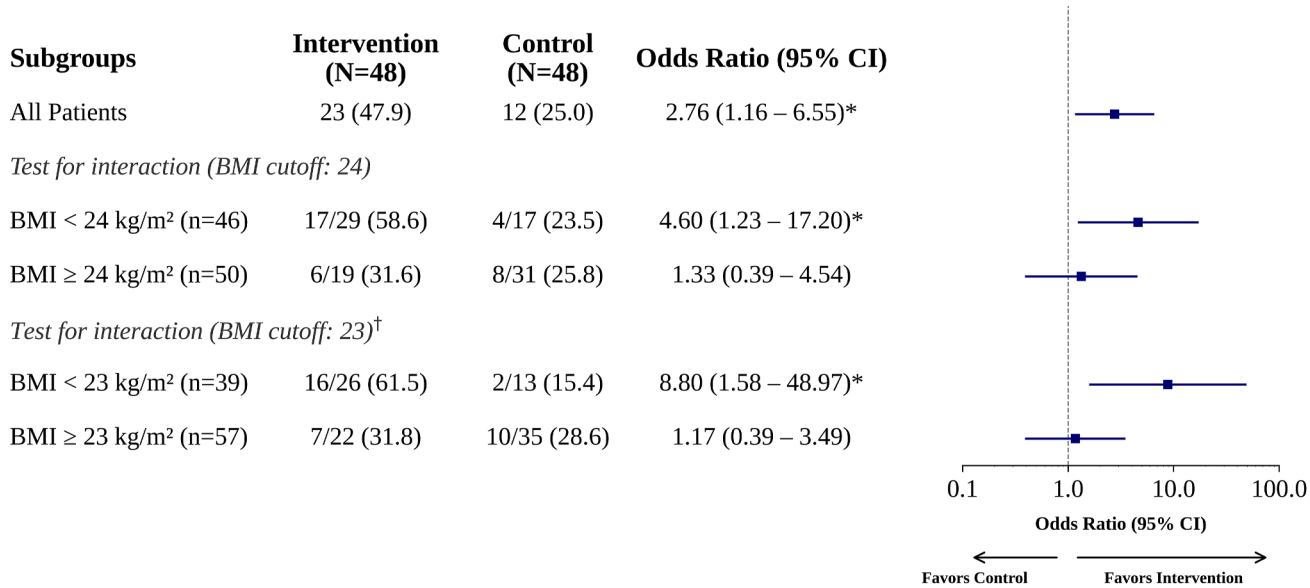


Figure 2. Forest plot of the intervention effect on SGA improvement, stratified by BMI <23 versus ≥23 kg/m^2 and BMI <24 versus ≥24 kg/m^2. The squares represent the odds ratios (ORs), and the horizontal lines indicate the 95% confidence intervals (CIs). The x-axis is presented on a logarithmic scale. **P* < .05; †*P* value for interaction < .05. SGA, subjective global assessment; BMI, body mass index.

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Table 4. Multivariable Logistic Regression Analysis of Factors Associated With SGA Improvement at 6 months

Variables	Model 1 Adjusted OR (95% CI)	*P* Value	Model 2 Adjusted OR (95% CI)	*P* Value	Model 3 Adjusted OR (95% CI)	*P* Value
Intervention group (vs. Control)	2.64 (1.09-6.39)	.031	2.32 (0.93-5.75)	.070	2.38 (0.95-5.98)	.066
Age (years)	0.99 (0.95-1.04)	.740	0.99 (0.95-1.04)	.765	0.99 (0.94-1.03)	.518
Sex (Male vs. Female)	0.81 (0.34-1.92)	.634	0.96 (0.39-2.37)	.936	1.87 (0.62-5.68)	.267
BMI (baseline, kg/m^2)	—	—	0.91 (0.79-1.04)	.152	—	—
Body weight (Baseline, kg)	—	—	—	—	0.94 (0.89-0.99)	.017

Adjusted OR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; SGA, subjective global assessment.

Model 1 was adjusted for intervention group, age, and sex. Model 2 was adjusted for intervention group, age, sex, and baseline BMI. Model 3 was adjusted for intervention group, age, sex, and baseline body weight. Baseline BMI was examined as a standardized anthropometric index commonly used in clinical practice, whereas baseline body weight was examined as an alternative body-size variable selected with reference to univariate analyses and clinical relevance.

energy derived from carbohydrate and lower proportions derived from protein and fat (all $P < .001$; Table S5).

Anthropometrics and Muscle Strength

Both groups showed significant increases in BMI (Table 2). However, the intervention group showed significant improvements in MAMC and HGS ($P < .05$). In contrast, the control group showed significant increases in HGS and TSF but not in MAMC ($P = .529$; Table 2, Table S4). These findings indicate different within-group patterns of anthropometric change over follow-up.

Body Composition

The intervention group showed no significant within-group changes in BIA-derived body-composition parameters over 6 months (Table 2, Table S4). Conversely, the control group showed significant increases in fat mass and body fat percentage, together with a decrease in total body water percentage (Table S4). At month 6, the intervention group had lower absolute fat mass than the control group (13.7 vs. 15.8 kg; $P = .022$; Table S5).

Laboratory Parameters and Renal Function

The intervention group showed a significant reduction in low-density lipoprotein cholesterol over 6 months (92.7-83.9 mg/dL; $P = .029$), and the change in high-density lipoprotein cholesterol was more favorable than in the control group ($P = .034$; Table 2, Table S8). Although eGFR declined in both groups over follow-up, linear mixed-effects modeling showed no significant between-group difference in the rate of eGFR decline (control slope: −0.92 [95% CI, −1.53 to −0.32] mL/min/1.73 m^2; intervention slope: −1.30 [95% CI, −1.90 to −0.70] mL/min/1.73 m^2; group-by-time interaction, $P = .381$; Table S9), suggesting no evidence of accelerated renal decline with the intervention. In contrast, the control group showed significant increases in serum urea nitrogen and decreases in serum albumin over follow-up ($P < .05$; Table 2).

Safety and Gastrointestinal Symptoms

No serious adverse events related to the intervention were identified. Both groups showed improvement in gastroesophageal reflux symptoms over follow-up, whereas improvement in "difficulty eating normal portions" was observed only in the intervention group (Table S4). At month 6, the intervention group had lower scores for difficulty eating normal portions than the control group ($P = .008$; Table S5). No significant between-group differences were observed for other gastrointestinal symptoms at month 6.

Discussion

This was an open-label, largely randomized trial analyzed according to the as-treated principle. Among adults with nondialysis CKD stages 3–5, adding a kidney-specific, high-energy, low-protein oral formula containing free amino acids, dietary fiber, vitamins, and minerals to dietitian-led counseling toward low-protein diet targets was associated with a higher proportion of participants achieving score-based SGA improvement over 6 months than counseling alone. The direction of this association remained similar in sensitivity analyses addressing the clinical ambiguity of within-category transitions from SGA score 6-7, and the apparent benefit was greatest among participants with lower baseline BMI. Secondary analyses also suggested a more favorable pattern of energy intake, macronutrient distribution, anthropometric change, and lipid change in the intervention group, whereas no significant between-group difference was observed in the slope of eGFR decline. Taken together, these findings support a potential nutritional benefit of this supplementation strategy without evidence of short-term renal harm.

In the revised multivariable analyses, the association between the intervention and SGA improvement remained directionally consistent after adjustment for baseline body size, although the effect estimate was attenuated. When baseline BMI was added to the model, the intervention effect became weaker, and BMI itself was not independently

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associated with SGA improvement. In the alternative model using baseline BW, the intervention effect remained similar in direction, and lower baseline BW was independently associated with SGA improvement. These findings suggest that the observed benefit of the intervention was not fully explained by baseline body-size imbalances alone. Rather, BMI-based and BW-based adjustment appeared to provide complementary information, with absolute BW in this cohort possibly capturing aspects of baseline nutritional status not fully reflected by height-adjusted BMI. This interpretation is also consistent with our subgroup analysis, in which the largest apparent benefit was observed among participants with baseline BMI <23 kg/m^2.

Our findings corroborate and extend previous work on renal-specific supplementation. Wu et al.[15] demonstrated that nonprotein supplements improved adherence to an LPD and exerted beneficial renal responses. Yang and Kelly et al.[14,16,17] also reported favorable nutritional or metabolic effects of renal-specific supplementation, although body composition findings across studies have not been entirely consistent.[14,17] In our study, the intervention group showed a more favorable anthropometric and functional pattern, including improvement in MAMC and HGS without a significant increase in fat mass, whereas the control group showed increases in TSF and fat mass over time.

A second issue concerns how improvement in SGA should be defined. We retained the primary analysis as a $\geq$ 1-point increase in the 7-point SGA because the study was designed to detect relatively small nutritional changes over 6 months, and the 7-point scale provides greater granularity than the original categorical SGA classification. SGA was originally introduced as a category-based clinical nutritional assessment,[29] whereas later CKD applications adopted the 7-point scale to better capture gradations of nutritional status and change over time.[30] Prior work has shown that the 7-point SGA is more sensitive than the conventional categorical SGA to short-term nutrition changes, and both KDOQI and KDIGO recognize it as a validated nutritional assessment tool in kidney disease.[4,7] In nondialysis CKD, Cuppari et al. also supported its validity for assessing PEW.[31] Because a transition from score 6 to 7 remains within SGA-A, however, its clinical meaning may be less distinct than broader cross-category changes.[32] We therefore performed 2 sensitivity analyses: one excluding 6-7 transitions and another classifying them as nonimprovement, thereby testing the robustness of the primary score-based finding under more conservative definitions.

The intervention may have improved nutritional status by increasing energy intake while maintaining a more protein-sparing dietary pattern during counseling toward LPD targets. However, the study formula contained not only energy and low protein but also free amino acids, dietary fiber, vitamins, and minerals; therefore, the present study cannot determine which component or combination contributed most to the observed changes. The favorable lipid findings may also have been influenced in part by the fatty acid composition of the formula, although these interpretations remain speculative.[27,33–37] Because no significant differences were observed in hs-CRP, hs-CRP-to-albumin ratio, or the triglyceride–glucose index, larger and longer studies are needed to clarify the underlying metabolic pathways.

From a clinical perspective, this strategy may be most relevant for selected patients with nondialysis CKD who have lower BMI, lower body mass, or difficulty maintaining adequate nonprotein energy intake during counseling toward LPD targets. The protocol was relatively practical in routine outpatient care, and no clear signal of excess adiposity, gastrointestinal intolerance, or accelerated eGFR decline was identified over 6 months. These findings suggest potential clinical utility in nutritionally vulnerable patients, although confirmation in larger and longer studies is needed.

This study has several strengths. The prospective design with fixed assessment points provides a feasible model for outpatient nutritional monitoring. Integrating SGA with HGS, MAMC, BIA, and biochemical panels allowed multidimensional assessment rather than reliance on a single marker. In addition, the focus on a homogeneous nondialysis CKD cohort in Taiwan and the inclusion of sensitivity analyses strengthen the relevance and interpretability of the findings.

This study has several limitations. Although participants were initially randomized, preintervention reassignment and as-treated analysis may have introduced selection bias and contributed to baseline imbalance. The sample size and number of outcome events were modest, and the 6-month follow-up was insufficient to evaluate longer-term kidney outcomes, hospitalization, or survival. Dietary protein intake was estimated from dietary recall rather than objective measures such as urinary nitrogen excretion, and the open-label design without placebo may have introduced expectancy, adherence, or reporting bias. In addition, some within-category SGA changes, particularly transitions from 6 to 7, may be less clinically distinct than broader category-based changes, and functional measures such as HGS may be influenced by factors other than nutrition alone. Finally, because the study formula contained multiple nutritional components, the specific contributors to the observed benefit could not be determined.

Conclusions

For nondialysis CKD patients receiving counseling toward an LPD, a kidney-specific high-energy, low-protein oral formula may help improve nutritional status without evidence of accelerated kidney function decline over 6 months. This approach may be most useful in nutritionally vulnerable patients, particularly those with lower BMI or limited nutritional reserve.

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Practical Application

For nondialysis CKD patients receiving counseling toward a LPD, a kidney-specific high-energy, low-protein oral formula may help improve nutritional status without evidence of accelerated kidney function decline over 6 months. This approach may be most useful in patients at higher risk for PEW, particularly those with lower BMI or limited nutritional reserve.

Author Contributions

All authors are responsible for the reliability, accuracy, and freedom from bias of the data and its interpretation in the discussion, and they provide final approval, ensuring the integrity of all aspects of the work. Yi-Hsiang Su, Hung-Lien Wu, and Chin-Chung Tseng contributed to the conceptualization of the work. Yi-Hsiang Su, Chia-Chun Lee, and Hung-Lien Wu contributed to data curation and formal analysis. Hung-Lien Wu contributed to funding acquisition. Yi-Hsiang Su, Chia-Chun Lee, Ming-Cheng Wang, Te-Hui Kuo, Hung-Lien Wu, and Chin-Chung Tseng contributed to investigation and project administration. Yi-Hsiang Su drafted the manuscript. Hung-Lien Wu and Chin-Chung Tseng critically revised the manuscript.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Gemini (Google) for language translation, text shorting, and the initial drafting of Python plotting scripts. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Acknowledgments

The authors would like to thank Peu-Wen Huang and the technical staff of the Division of Nephrology, National Cheng Kung University Hospital, for their skillful secretarial support.

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jrn.2026.06.009.

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