



# Very low protein diet plus ketoacid analogs of essential amino acids supplement to retard chronic kidney disease progression

Bancha Satirapoj, Peerapong Vongwattana, Ouppatham Supasyndh

Division of Nephrology, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand

**Background:** A very low protein diet (VLPD) with ketoacid analogs of essential amino acids (KA/EAA) administration can remarkably influence protein synthesis and metabolic disturbances of patients with advanced chronic kidney disease (CKD), and may also slow the decline in renal function.

**Methods:** A retrospective cohort study was carried out to monitor renal progression and metabolic and nutritional status among 140 patients with CKD stage III or IV. One group ( $n = 70$ ) was on a low protein diet (LPD) with 0.6 g of protein intake, and another group ( $n = 70$ ) was on a VLPD with 0.3 g of protein and KA/EAA supplementation of 100 mg/kg/day for 12 months.

**Results:** At 12-month follow-up, estimated glomerular filtration rate (GFR) significantly decreased from  $41.6 \pm 10.2$  to  $36.4 \pm 8.8$  mL/min/1.73 m<sup>2</sup> ( $P < 0.001$ ) and urine protein increased from  $0.6 \pm 0.5$  to  $0.9 \pm 1.1$  g/day ( $P = 0.017$ ) in the LPD group, but no significant changes in estimated GFR and urine protein were found in the VLPD plus KA/EAA group. A significant mean difference in rate of change in estimated GFR ( $-5.2 \pm 3.6$  mL/min/1.73 m<sup>2</sup> per year;  $P < 0.001$ ) was observed between the two groups. After Cox regression analysis, treatment with VLPD plus KA/EAA significantly protected against the incidence of declining GFR  $> 10\%$  annually (adjusted hazard ratio, 0.42; 95% confidence interval, 0.23–0.79;  $P = 0.006$ ) and significant correlations were found between using VLPD plus KA/EAA and increased GFR.

**Conclusion:** VLPD supplementation with KA/EAA is associated with delayed renal progression while preserving the nutritional status in the patients with CKD. Co-administration of VLPD and KA/EAA may prove an effective alternative to conservative management of CKD.

**Keywords:** Chronic renal insufficiency, Ketoanalog supplement, Protein-restricted diet

## Introduction

Ketoacid analogs of essential amino acids (KA/EAA) are prescribed in predialysis patients with chronic kidney disease (CKD) to lower generation of toxic metabolic products and improve nutritional status [1,2]. Because KA/EAA lack the amino group bound to the alpha carbon of an amino acid, a KA/EAA diet could convert their respective amino acids without providing additional nitrogen. The beneficial effects of protein restriction supplemented with ketoacid on the progression of CKD are multifactorial and may include decreasing nitrogen

Received June 7, 2018; Revised July 29, 2018;

Accepted August 13, 2018

Correspondence: Bancha Satirapoj

Division of Nephrology, Department of Medicine, Phramongkutklao Hospital and College of Medicine, 315 Rajavithi Road, Phaya Thai, Bangkok 10400, Thailand. E-mail: [satirapoj@yahoo.com](mailto:satirapoj@yahoo.com)  
ORCID: <https://orcid.org/0000-0002-8881-0942>

Copyright © 2018 by The Korean Society of Nephrology

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

waste, oxidative stress and inflammatory response including transforming growth factor-beta and protection against hemodynamic changes in glomerular hyperfiltration [3–5]. Among patients with CKD, ingestion of oral-specific renal formula may require an increase in dietary energy and fiber intake as well as decreased dietary protein intake [6].

Dietary protein plays an important role in the progression of CKD, and a low protein diet (LPD) is recommended to patients with advanced CKD to slow the decline in glomerular filtration rate (GFR) [7]. Additionally, several clinical trials and recent meta-analysis have documented that very low protein diets (VLPD) supplemented with KA/EAA preserve the rate of progression of advanced CKD [8–10] and delay the need for long-term dialysis treatment among patients with advanced CKD [11,12]. However, an MDRD study indicated that only a prescribed dietary protein intake of 0.6 g/kg/day, but not VLPD plus KA/EAA treatment, reduced the decline in GFR among patients with advanced CKD with GFR less than 25 mL/min/1.73 m<sup>2</sup> [13]. Moreover, in long-term follow-up of the MDRD study, VLPD plus KA/EAA treatment did not delay progression to dialysis or transplantation [14]. Consequently, no definitive conclusions have been reached on the role of protein-restricted regimens plus ketoacid analogs in slowing the loss of GFR among patients with CKD stage III, particularly in the era of more vigorous blood pressure with renin angiotensin aldosterone system inhibitors and tight glycemic control [15]. This retrospective study was designed to test the hypothesis that administering VLPD plus KA/EAA would decrease renal progression among patients with CKD compared with treatment by LPD.

## Methods

The patient's data from August 2010 and January 2015 were collected retrospectively at the Phramongkutklao Hospital in Bangkok, Thailand. The study was approved by the Institutional Review Board (R089h/57) of Phramongkutklao Hospital.

### Subjects

Inclusion criteria were age 18 years or older and nondialysis patients with CKD stage III or IV. Only patients with

regular follow-up based on medical reports and prescriptions that had been recorded in our hospital electronic database for a period of 12 months before the study were recruited for the screening visit. Patients with active malignancy, severe heart, lung or liver disease, stroke, chronic infection, protein-energy wasting based on anthropometric data and laboratory data, especially serum albumin < 3.5 g/dL, pregnancy, any immunological or inflammatory disorders or known history of KA/EAA hypersensitivity were excluded from the study.

All patients with CKD received multidisciplinary care team treatment including renal dietitian consultations. According to the standard of care, patients with CKD stage III or IV were followed in nephrology clinics every three months. Nutritional compliance with dietary protein intake was measured using a diet record and analyzed using standard food composition tables. According to the medical history records, eligible patients were divided in two groups based on their regimen 12 months before the study as described below. The treatment group (n = 70) was prescribed a VLPD of 0.3 g of protein and KA/EAA 100 mg/kg/day and the control group (n = 70) was prescribed an LPD of 0.6 g of protein and no KA/EAA. The KA/EAA used in our study was Ketosteril (Fresenius Kabi, Bad Homburg vor der Höhe, Germany), 630 mg/tablet prescribed at 1 tablet/5 kg body weight daily. The prescriptions were made by the nephrologists monitoring the patients in the predialysis period to maintain the nutritional biochemical parameters.

The primary outcome was the differences in estimated GFR decline rates between the treatment and control groups. The secondary outcomes were the differences of the amount of proteinuria that was evaluated using urine protein-to-creatinine ratio and biochemical profiles between the two groups. Patients with significant CKD progression were defined as estimated GFR decline > 10% annually from baseline.

### Clinical and laboratory monitoring

Medical history, physical examinations and biochemical tests were taken at the first visit before starting treatment. All routine laboratory tests, including assays for plasma levels of hemoglobin, albumin, potassium, creatinine, calcium, phosphate and estimated GFR using the 2009 CKD-EPI creatinine equation and staging accord-

ing to The Kidney Disease: Improving Global Outcomes (KDIGO) 2012, were performed at baseline and at the end of the study. Adverse events that were or were not considered related to treatment were monitored from medical data sheets.

### Statistical analysis

Measured values of the results were expressed in mean with standard deviation and percentage. The paired *t* test was used to compare the change of parameters within group at baseline and 12 months. Parameters were compared between groups at baseline and 12 months using the chi-square test, Fisher's exact test and Student *t* test. ANCOVA analyses with baseline value of treatment period as covariate were used to assess for between-group mean differences at 12 months. We used Cox regression to analyze the association between declining GFR and VLPD with KA/EAA administration, unadjusted and then adjusted for age, diabetes, hypertensive nephropathy, body mass index (BMI), systolic blood pressure, baseline GFR, baseline proteinuria, angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and statin treatment. Additionally, we used multivariate regression to analyze the association between change of GFR and VLPD with KA/EAA administration after adjusting for other confounding factors. Statistical analyses were performed using the SPSS version 15 program for Windows (SPSS Inc., Chicago, IL, USA). A *P* value less than 0.05 was considered statistically significant.

## Results

A total of 282 patients with CKD stage III or IV were screened for possible study enrollment. One hundred forty patients were eligible according to the entry criteria and received either LPD or VLPD plus KA/EAA treatment. In the LPD and VLPD plus KA/EAA groups, average age was  $68.4 \pm 10.6$  and  $73.7 \pm 9.3$  years, respectively ( $P = 0.002$ ), and male prevalence was 44.9% and 27.1%, respectively ( $P = 0.029$ ). Type 2 diabetes prevalence differed in the two groups ( $P = 0.042$ ), being 61.4% and 44.3% in the LPD and VLPD plus KA/EAA groups, respectively. Prescription medications including ACEI/ARB (61.4% vs. 41.4%,  $P = 0.018$ ) and statins (84.3% vs. 60%,  $P = 0.001$ ) were found to be higher in LPD group. The aver-

age dose of KA/EAA in VLPD treatment was  $11.2 \pm 1.3$  tablets per day. Characteristics of the patients are shown in Table 1. No significant differences were found in body weight, systolic blood pressure, primary renal diseases, the amount of the proteinuria, hemoglobin, serum potassium, bicarbonate or calcium, but significantly increased BMI, diastolic blood pressure and serum phosphate were found in the LPD group.

### Renal function and proteinuria after treatments

In the LPD and VLPD plus KA/EAA groups, average estimated GFR was  $41.6 \pm 10.2$  and  $39.1 \pm 9.2$  years, respectively ( $P = 0.131$ ). The VLPD plus KA/EAA group exhibited no significant change in estimated GFR levels from  $39.1 \pm 9.2$  mL/min/1.73 m<sup>2</sup> at baseline to  $38.9 \pm 12.0$  mL/min/1.73 m<sup>2</sup> at 12 months (Table 2), but the LPD group with or without ACEI/ARB presented a significant change in estimated GFR levels from  $41.6 \pm 10.2$  mL/min/1.73 m<sup>2</sup> at baseline to  $36.8 \pm 8.8$  mL/min/1.73 m<sup>2</sup> at 12 months ( $P < 0.001$ ) (Table 2). GFR levels during the 12-month follow-up declined on average by  $-5.2 \pm 3.6$  mL/min/1.73 m<sup>2</sup> in the LPD group and by  $-0.3 \pm 6.8$  mL/min/1.73 m<sup>2</sup> in the VLPD plus KA/EAA group ( $P < 0.001$ ) (Table 3, Fig. 1). A significant mean difference in rate of change in estimated GFR ( $-5.2 \pm 3.6$  mL/min/1.73 m<sup>2</sup> per year;  $P < 0.001$ ) was observed between the two groups. Similarly, these results were found in the change of blood urea nitrogen ( $22.8 \pm 7.3$  vs.  $24.3 \pm 7.1$  mg/dL,  $P = 0.031$ ) and serum creatinine ( $1.6 \pm 0.4$  vs.  $1.8 \pm 0.4$ ,  $P < 0.001$ ) in the LPD group after 12 months of treatment. Moreover, the LPD group with or without ACEI/ARB showed a significant increase in urine protein levels from  $0.6 \pm 0.5$  g/gCr at baseline to  $0.9 \pm 1.1$  g/gCr at 12 months ( $P = 0.017$ ) (Table 2, Fig. 1), but no significant difference was observed in mean change in urine protein between the two groups (Table 3).

Table 4 demonstrates the results of Cox regression analysis of significant GFR decline with some potential confounding parameters. The risk for GFR decline > 10% annually was lower with VLPD plus KA/EAA compared with LPD (hazard ratio [HR], 0.48; 95% confidence interval [CI] 0.28–0.82;  $P = 0.008$ ). This protective effect was independent of age, diabetes, hypertensive nephropathy, ACEI/ARB, statins, BMI, systolic blood pressure, baseline GFR and proteinuria (adjusted HR, 0.42; 95% CI, 0.23–0.79;  $P = 0.006$ ).

**Table 1.** Characteristics of the study populations between LPD and VLPD with KA/EAA

Variable	LPD (n = 70)	VLPD + KA/EAA (n = 70)	P value
Age (yr)	68.4 ± 10.6	73.7 ± 9.3	0.002
Sex, male	32 (44.9)	19 (27.1)	0.029
Body weight (kg)	67.1 ± 11.7	65.1 ± 12.6	0.336
Body mass index (kg/m <sup>2</sup> )	25.2 ± 3.5	23.8 ± 4.3	0.035
Systolic blood pressure (mmHg)	137.0 ± 11.2	133.4 ± 16.6	0.131
Diastolic blood pressure (mmHg)	78.2 ± 8.5	73.9 ± 9.4	0.006
Dietary protein intake (g/d)	0.6 ± 0.1	0.3 ± 0.1	0.001
Primary renal disease (%)			
Diabetic nephropathy	41 (58.6)	31 (44.3)	0.091
Glomerular disease	6 (8.6)	1 (1.4)	0.116
Hypertension	12 (17.1)	24 (34.3)	0.020
ADPKD	1 (1.4)	0 (0)	1.000
Underlying disease			
Type 2 diabetes	43 (61.4)	31 (44.3)	0.042
Hypertension	68 (97.1)	65 (92.9)	0.245
Dyslipidemia	68 (97.1)	63 (90.0)	0.165
Cerebrovascular disease	7 (10.0)	2 (2.9)	0.165
Coronary heart disease	18 (25.7)	12 (17.1)	0.217
Medications			
ACEI/ARB	43 (61.4)	29 (41.4)	0.018
Statins	59 (84.3)	42 (60.0)	0.001
Recombinant EPO	3 (4.3)	9 (12.9)	0.070
BUN (mg/dL)	22.8 ± 7.3	22.2 ± 6.8	0.636
Serum creatinine (mg/dL)	1.6 ± 0.4	1.7 ± 0.4	0.309
Glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	41.6 ± 10.2	39.1 ± 9.2	0.131
24 hr urine protein (g)	0.6 ± 0.5	0.4 ± 0.4	0.134
> 1 g/d	3 (4.3)	1 (1.4)	0.581
> 150 mg/d	23 (32.9)	20 (28.6)	0.302
Hemoglobin (g/dL)	12.1 ± 1.8	12.3 ± 1.9	0.600
Potassium (mEq/L)	4.3 ± 0.5	4.3 ± 0.6	0.991
Bicarbonate (mEq/L)	25.2 ± 3.1	25.5 ± 2.9	0.503
Calcium (mg/dL)	9.3 ± 0.5	9.4 ± 0.5	0.184
Phosphate (mg/dL)	3.7 ± 0.6	3.4 ± 0.5	0.001

Data are presented as mean ± standard deviation and number (%).

ACEI, angiotensin converting enzyme inhibitor; ADPKD, autosomal dominant polycystic kidney disease; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; KA/EAA, ketoacid analogues of essential amino acids; LPD, low protein diet; VLPD, very LPD.

Univariate analysis was performed to assess the relationship between clinical parameters with change of GFR. VLPD plus KA/EEA compared with LPD was positively correlated with increased estimated GFR, whereas diabetes, baseline estimated GFR, and proteinuria were negatively correlated with increased estimated GFR. After multiple regression analyses, significant correlations were found among age, baseline estimated GFR, BMI, and use of VLPD plus KA/EEA with change in GFR (Table 5).

#### *Changes in metabolic profiles and electrolytes after treatment*

During the 12-month study, the LPD group exhibited significantly increased plasma potassium and decreased plasma phosphate ( $P < 0.001$ ), but no significant difference was observed regarding mean changes in serum albumin, hemoglobin, potassium, bicarbonate, calcium and phosphate levels between the two groups (Table 5).

**Table 2.** Changes in renal and metabolic parameters after 12 months of treatment

Parameter	LPD (n = 70)			VLPD + KA/EAA (n = 70)		
	Baseline	12 mo	P value	Baseline	12 mo	P value
BUN (mg/dL)	22.8 ± 7.3	24.3 ± 7.1	0.031	22.2 ± 6.76	21.9 ± 7.0	0.778
Creatinine (mg/dL)	1.6 ± 0.4	1.8 ± 0.4	< 0.001	1.7 ± 0.3	1.7 ± 0.5	0.175
GFR (mL/min/1.73 m <sup>2</sup> )	41.6 ± 10.2	36.8 ± 8.8	< 0.001	39.1 ± 9.2	38.9 ± 12.0	0.742
24 hr urine protein (g)	0.6 ± 0.5	0.9 ± 1.1	0.017	0.2 ± 0.4	0.3 ± 0.5	0.450
Albumin (g/dL)	4.2 ± 0.4	4.1 ± 0.4	0.155	4.2 ± 0.4	4.2 ± 0.4	0.578
Hemoglobin (g/dL)	12.1 ± 1.8	11.9 ± 1.7	0.333	12.3 ± 1.9	12.3 ± 1.8	0.307
Potassium (mEq/L)	4.3 ± 0.5	4.5 ± 0.5	0.016	4.3 ± 0.6	4.3 ± 0.4	0.308
Bicarbonate (mEq/L)	25.2 ± 3.1	24.7 ± 2.9	0.234	25.5 ± 2.9	25.6 ± 2.4	0.826
Calcium (mg/dL)	9.3 ± 0.5	9.3 ± 0.5	0.482	9.4 ± 0.5	9.4 ± 0.5	0.310
Phosphate (mg/dL)	3.7 ± 0.6	3.5 ± 0.6	0.011	3.4 ± 0.5	3.3 ± 0.5	0.107
Renal outcomes in subgroups of CKD staging						
CKD III (GFR 30–59 mL/min/1.73 m <sup>2</sup> ) (n = 113)						
GFR (mL/min/1.73 m <sup>2</sup> )	44.64 ± 8.45	38.98 ± 7.38	< 0.001	41.86 ± 7.46	41.55 ± 10.95	0.758
24 hr urine protein (g)	0.56 ± 0.54	0.98 ± 1.14	0.061	0.16 ± 0.1	0.16 ± 0.1	0.946
CKD IV (GFR 15–29 mL/min/1.73 m <sup>2</sup> ) (n = 27)						
GFR (mL/min/1.73 m <sup>2</sup> )	27.06 ± 3.03	24.32 ± 3.46	0.002	27.77 ± 1.5	27.27 ± 5.26	0.680
24 hr urine protein (g)	0.51 ± 0.45	0.92 ± 0.95	0.086	0.62 ± 0.98	1.12 ± 0.98	0.575
Renal outcomes in patients with ACEI/ARB (n = 72)						
GFR (mL/min/1.73 m <sup>2</sup> )	42.86 ± 9.25	38.18 ± 8.55	< 0.001	42.79 ± 8.2	40.69 ± 11.55	0.155
24 hr urine protein (g)	0.58 ± 0.56	0.83 ± 1.07	0.191	0.17 ± 0.11	0.15 ± 0.08	0.407
Renal outcomes in patients without ACEI/ARB (n = 68)						
GFR (mL/min/1.73 m <sup>2</sup> )	39.66 ± 11.57	33.74 ± 8.7	< 0.001	36.54 ± 9.07	37.57 ± 12.3	0.265
24 hr urine protein (g)	0.48 ± 0.4	1.24 ± 1.11	0.038	0.3 ± 0.59	0.52 ± 0.73	0.415

Data are presented as mean ± standard deviation.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BUN, blood urea nitrogen; CKD, chronic kidney disease; GFR, glomerular filtration rate; KA/EAA, ketoacid analogues of essential amino acids; LPD, low protein diet; VLPD, very LPD.

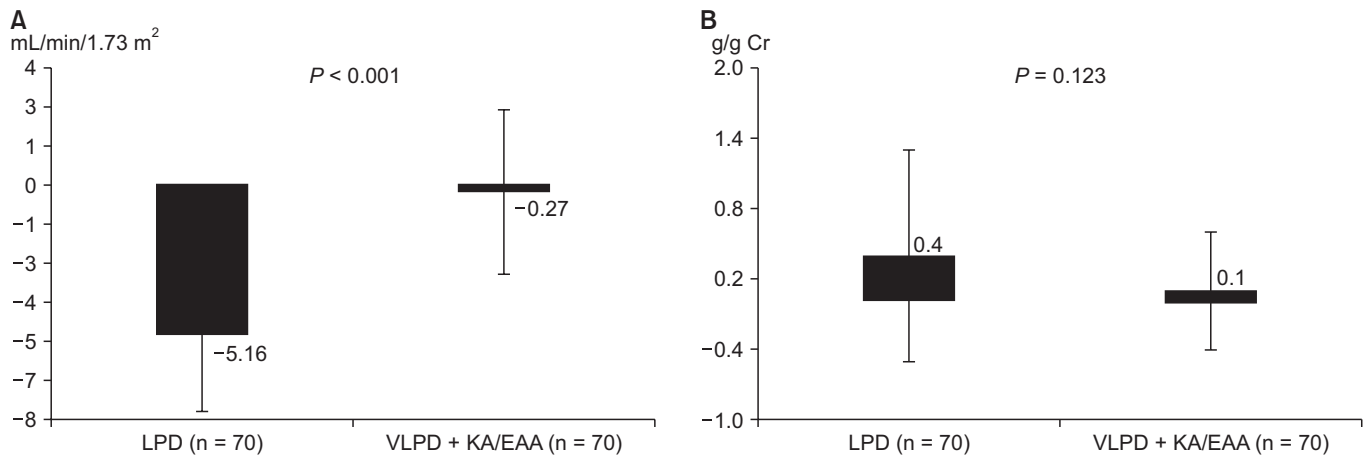
**Table 3.** Mean changes in renal and metabolic parameters between the two groups

Parameter	LPD (n = 70)	VLPD + KA/EAA (n = 70)	Between-group differences*		
			Mean ± SD change	F	P value
BUN (mg/dL)	1.5 ± 5.8	0.2 ± 6.9	1.8 ± 2.9	2.649	0.106
Creatinine (mg/dL)	0.2 ± 0.1	0.1 ± 0.3	0.1 ± 0.0	7.717	0.006
GFR (mL/min/1.73 m <sup>2</sup> )	−5.2 ± 3.6	−0.3 ± 6.8	−4.9 ± 6.0	28.168	< 0.001
24 hr urine protein (g)	0.4 ± 0.9	0.1 ± 0.5	0.3 ± 0.4	1.935	0.171
Albumin (g/dL)	−0.1 ± 0.3	0.1 ± 0.4	−0.1 ± 0.3	1.622	0.206
Hemoglobin (g/dL)	−0.1 ± 1.2	0.2 ± 1.1	−0.3 ± 1.0	1.981	0.162
Potassium (mEq/L)	0.2 ± 0.6	0.1 ± 0.5	0.1 ± 0.3	1.401	0.239
Bicarbonate (mEq/L)	−0.5 ± 3.3	0.1 ± 3.2	−0.6 ± 2.7	1.042	0.309
Calcium (mg/dL)	−0.1 ± 0.5	0.1 ± 0.4	−0.1 ± 0.4	1.461	0.229
Phosphate (mg/dL)	−0.2 ± 0.6	−0.1 ± 0.3	−0.2 ± 0.6	2.633	0.108

Data are presented as mean ± standard deviation (SD).

BUN, blood urea nitrogen; GFR, glomerular filtration rate; KA/EAA, ketoacid analogues of essential amino acids; LPD, low protein diet; VLPD, very LPD.

\*Using ANCOVA.



**Figure 1. Renal function and proteinuria after 12 months of treatment.** Mean changes of estimated glomerular filtration rate (A) and proteinuria (B) presented a significantly worsening progression in the low protein diet (LPD) group ( $P < 0.05$ ) compared with the very LPD (VLPD) + ketoacid analogues of essential amino acids (KA/EAA) group.

**Table 4. Influence of various factors on glomerular filtration rate (GFR) decline > 10% within 12 months**

Variable	Unadjusted HR	95% CI	P value	Adjusted HR	95% CI	P value
VLPD with KA/EAA vs. LPD	0.48	0.28–0.82	0.008	0.42	0.23–0.79	0.006
Age	0.99	0.97–1.02	0.644	1.00	0.98–1.03	0.856
Diabetes mellitus	1.21	0.72–2.03	0.464	1.13	0.64–1.98	0.675
Hypertensive nephropathy	1.50	0.37–6.14	0.573	1.38	0.31–6.12	0.670
ACEI/ARB	0.91	0.55–1.52	0.727	0.80	0.46–1.38	0.426
Statins	1.13	0.63–2.04	0.677	0.93	0.5–1.72	0.811
BMI ( $\text{kg}/\text{m}^2$ )	0.99	0.93–1.06	0.746	0.97	0.9–1.05	0.458
Systolic blood pressure (mmHg)	1.00	0.98–1.02	0.792	1.00	0.98–1.02	0.801
Baseline GFR	0.99	0.97–1.02	0.536	0.99	0.97–1.02	0.587
Baseline urine protein	1.55	0.72–3.37	0.266			

Adjusted for age, diabetes, hypertensive nephropathy, body mass index (BMI), systolic blood pressure, baseline GFR, baseline proteinuria, ACEI/ARB and statin treatment.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio; KA/EAA, ketoacid analogues of essential amino acids; LPD, low protein diet; VLPD, very LPD.

No serious complications related to protein intake were observed and none of the patients received acute dialysis during the study.

## Discussion

The present study constitutes a retrospective clinical trial of VLPD plus KA/EAA supplementation on renal function among patients with CKD stage III or IV. VLPD, when supplemented with KA/EAA, could decrease the rate of CKD progression among these patients when compared with LPD treatment through a reduced dietary protein intake and controlled metabolic waste products

during CKD progression.

Decreased dietary protein intake was associated with a retardation of GFR loss and reduction in proteinuria among predialysis patients with CKD [16–18]. However, it exposed patients to the risk of protein malnutrition. In experimental CKD models, high protein intake induces renal proinflammatory cytokines, profibrotic growth factors, oxidative stress, glomerular hyperfiltration and glomerular hypertrophy, and results in glomerular sclerosis, mesangial matrix expansion and proteinuria [19]. Inversely, LPD supplemented with ketoacids was more effective than LPD alone in protecting kidney function from oxidative stress injury in remnant kidney tissue [20]. As

**Table 5.** Univariate and multivariate regression analyses demonstrating factors showing correlation with change in glomerular filtration rate (GFR) within 12 months

Variable	Univariate		Multivariate	
	R	P value	Standardized coefficient (95% CI)	P value
VLPD with KA/EAA vs. LPD	0.412	0.001	7.39 (4.31 to 10.47)	0.001
Age	-0.003	0.971	-0.18 (-0.32 to 0.05)	0.010
Diabetes mellitus	-0.201	0.017	-1.8 (-5.47 to 1.87)	0.326
Hypertensive nephropathy	0.090	0.291	-3.1 (-8.28 to 2.08)	0.232
ACEI/ARB	-0.161	0.058	1.22 (-1.63 to 4.06)	0.390
Statins	0.006	0.942	1.21 (-2.09 to 4.51)	0.463
Body mass index (kg/m <sup>2</sup> )	-0.050	0.557	0.43 (0.05 to 0.81)	0.027
Systolic blood pressure (mmHg)	0.041	0.628	0.07 (-0.05 to 0.18)	0.248
Baseline GFR	-0.167	0.048	-0.15 (-0.29 to 0.01)	0.041
Baseline urine protein	-0.309	0.039	-2.35 (-5.21 to 0.52)	0.105

Independent variables in the multivariate model were chosen using a stepwise regression analysis where all significant variables listed in the univariate analysis were included.

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; KA/EAA, ketoacid analogues of essential amino acids; LPD, low protein diet; VLPD, very LPD.

a consequence, VLPD with KA/EAA has been supposed to protect against the progression of CKD and preserve residual renal function, slowing the GFR decline toward end-stage renal disease [21]. Strategies to avoid protein malnutrition include supplementing decreased protein intake with essential amino acids for CKD populations. Our results showed a better preservation of GFR over 12 months among patients that were prescribed VLPD supplemented with KA/EAA, but not among those that were prescribed LPD alone. Similar to related retrospective, prospective, or randomized studies, VLPD plus KA/EAA preserved GFR and delayed the need for long term dialysis treatment among patients with advanced CKD [8–12]. Recently, a well-defined, randomized, controlled trial demonstrated that vegetarian VLPD supplemented with ketoacid analogs delayed dialysis initiation among patients with advanced CKD with GFR less than 20 to 30 mL/min/1.73 m<sup>2</sup> by ameliorating metabolic disturbances [22]. Finally, recent meta-analyses and real clinical practice in nephrology registry supported that VLPD or LPD, supplemented with ketoacid analogs, significantly prevented the deterioration of GFR [10,23,24]. Related clinical trials were investigated among patients with very late stages of CKD or CKD stage V, who wished to defer dialysis treatment. However, our study included CKD stage III with an average GFR of 40 mL/min/1.73 m<sup>2</sup>. Therefore, the positive role of VLPD plus KA/EAA treatment might

become more apparent in CKD stage III without dialysis.

Our results did not demonstrate a significant change in proteinuria after 12 months of treatment. However, administration of VLPD plus KA/EAA tended to lower proteinuria levels, while LPD treatment significantly increased proteinuria levels. Related studies have indicated an association between a restricted protein diet with or without KA/EAA and reduced proteinuria levels among patients with CKD [25–27]. The anti-proteinuric response to restricted dietary protein intake was reported among patients with significant proteinuria levels > 1 g/day and high baseline serum phosphate [25–27]. The beneficial effects of KA/EAA treatment on proteinuria was limited in our study because of the differences in patient population, especially low baseline urine protein and normal serum phosphate levels among patients in our study.

VLPD supplemented with ketoacid analogs may serve a role in the conservative management and improved metabolic profiles among patients with CKD. Current evidence indicates that restricted dietary protein intake improves metabolic surrogates of CKD, including azotemia, bone and mineral disorder and acidosis [28]. Related studies have shown higher serum bicarbonate, higher serum calcium and lower phosphorus levels among those receiving VLPD plus KA/EAA compared with LPD [22,29]. However, we did not observe any significant differences in changes of bicarbonate, calcium and phosphate lev-

els between VLPD and LPD groups, because of different population settings, especially in CKD stage III with normal metabolic disturbances at baseline.

This study had several limitations. First, the patient selection was not random and could have contained selection bias, including diet compliance, other nephroprotective therapies, sodium restriction and optimal glycemic control. However, factors affecting renal progression other than dietary protein intake were included and analyzed before and during the study and the confounding factors were considered in multiple regression analysis. Secondly, this study included a relatively small number of patients and short follow-up time. The short follow-up time may explain the nonsignificant differences in main renal outcomes, including renal replacement therapy. Thirdly, dietary protein intake was assessed using a three-day food diary, so we cannot exclude the possibility of some patients misjudging intake. As a retrospective study using medical electronic databases, we were unable to confirm whether patients actually took the dispensed medications. Finally, the generalizability of our data is limited to a CKD population with advanced age at 70 years. These results may not be applicable to all patients with CKD.

In conclusion, VLPD plus KA/EAA treatment was associated with even greater preservation of renal function in CKD stage III–IV. KA/EAA supplementation provides an additional therapeutic intervention to slow CKD progression. The effect of this treatment on long-term renal function among patients with CKD should be further assessed using larger patient populations and longer treatment periods.

### Conflicts of Interest

This study was supported by the Department of Medicine, Phramongkutklao Hospital and College of Medicine. All authors have no conflicts of interest to declare.

### Acknowledgments

The authors wish to acknowledge the contributions of the following individuals to this study: staff in the Division of Nephrology and Biomedical Clinical Research Center in Phramongkutklao Hospital.

### References

- [1] Walser M. Does prolonged protein restriction preceding dialysis lead to protein malnutrition at the onset of dialysis? *Kidney Int* 44:1139-1144, 1993
- [2] Feiten SF, Draibe SA, Watanabe R, et al. Short-term effects of a very-low-protein diet supplemented with ketoacids in nondialyzed chronic kidney disease patients. *Eur J Clin Nutr* 59:129-136, 2005
- [3] Gao X, Huang L, Grosjean F, et al. Low-protein diet supplemented with ketoacids reduces the severity of renal disease in 5/6 nephrectomized rats: a role for KLF15. *Kidney Int* 79:987-996, 2011
- [4] Brodsky IG, Robbins DC, Hiser E, Fuller SP, Fillyaw M, Devlin JT. Effects of low-protein diets on protein metabolism in insulin-dependent diabetes mellitus patients with early nephropathy. *J Clin Endocrinol Metab* 75:351-357, 1992
- [5] Yang X, Yang M, Cheng M, et al. Effects of low-protein diets supplemented with ketoacid on expression of TGF- $\beta$  and its receptors in diabetic rats. *Biomed Res Int* 2015:873519, 2015
- [6] Satirapoj B, Prapakorn J, Punpanich D, Pongsuparbchon C, Supasynndh O. The effect of ONCE Renal on minerals and electrolytes in predialysis patients with chronic kidney disease. *Int J Nephrol Renovasc Dis* 9:81-86, 2016
- [7] Kasiske BL, Lakatua JD, Ma JZ, Louis TA. A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 31:954-961, 1998
- [8] Prakash S, Pande DP, Sharma S, Sharma D, Bal CS, Kulkarni H. Randomized, double-blind, placebo-controlled trial to evaluate efficacy of ketodiet in predialytic chronic renal failure. *J Ren Nutr* 14:89-96, 2004
- [9] Walser M, Hill S, Ward L. Progression of chronic renal failure on substituting a ketoacid supplement for an amino acid supplement. *J Am Soc Nephrol* 2:1178-1185, 1992
- [10] Jiang Z, Zhang X, Yang L, Li Z, Qin W. Effect of restricted protein diet supplemented with keto analogues in chronic kidney disease: a systematic review and meta-analysis. *Int Urol Nephrol* 48:409-418, 2016
- [11] Brunori G, Viola BF, Parrinello G, et al. Efficacy and safety of a very-low-protein diet when postponing dialysis in the elderly: a prospective randomized multicenter controlled study. *Am J Kidney Dis* 49:569-580, 2007
- [12] Bellizzi V, Chiodini P, Cupisti A, et al. Very low-protein diet plus ketoacids in chronic kidney disease and risk of death during end-stage renal disease: a historical cohort con-



- trolled study. *Nephrol Dial Transplant* 30:71-77, 2015
- [13] Klahr S, Levey AS, Beck GJ, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. *N Engl J Med* 330:877-884, 1994
- [14] Menon V, Kopple JD, Wang X, et al. Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis* 53:208-217, 2009
- [15] Shah AP, Kalantar-Zadeh K, Kopple JD. Is there a role for ketoacid supplements in the management of CKD? *Am J Kidney Dis* 65:659-673, 2015
- [16] Levey AS, Adler S, Caggiula AW, et al. Effects of dietary protein restriction on the progression of advanced renal disease in the Modification of Diet in Renal Disease Study. *Am J Kidney Dis* 27:652-663, 1996
- [17] Levey AS, Greene T, Beck GJ, et al. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. *J Am Soc Nephrol* 10:2426-2439, 1999
- [18] Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 123:754-762, 1995
- [19] Tovar-Palacio C, Tovar AR, Torres N, et al. Proinflammatory gene expression and renal lipogenesis are modulated by dietary protein content in obese Zucker fa/fa rats. *Am J Physiol Renal Physiol* 300:F263-F271, 2011
- [20] Gao X, Wu J, Dong Z, et al. A low-protein diet supplemented with ketoacids plays a more protective role against oxidative stress of rat kidney tissue with 5/6 nephrectomy than a low-protein diet alone. *Br J Nutr* 103:608-616, 2010
- [21] Bellizzi V, Calella P, Carrero JJ, Fouque D. Very low-protein diet to postpone renal failure: Pathophysiology and clinical applications in chronic kidney disease. *Chronic Dis Transl Med* 4:45-50, 2018
- [22] Garneata L, Stancu A, Dragomir D, Stefan G, Mircescu G. Ketoanalogue-supplemented vegetarian very low-protein diet and CKD progression. *J Am Soc Nephrol* 27:2164-2176, 2016
- [23] You JH, Ming WK, Lin WA, Tarn YH. Early supplemented low-protein diet restriction for chronic kidney disease patients in Taiwan - A cost-effectiveness analysis. *Clin Nephrol* 84:189-196, 2015
- [24] Zemchenkova A, Konakova IN. Efficacy of the Essential Amino Acids and Keto-Analogues on the CKD progression rate in real practice in Russia - city nephrology registry data for outpatient clinic. *BMC Nephrol* 17:62, 2016
- [25] Chauveau P, Combe C, Rigalleau V, Vendrely B, Aparicio M. Restricted protein diet is associated with decrease in proteinuria: consequences on the progression of renal failure. *J Ren Nutr* 17:250-257, 2007
- [26] Gansevoort RT, de Zeeuw D, de Jong PE. Additive antiproteinuric effect of ACE inhibition and a low-protein diet in human renal disease. *Nephrol Dial Transplant* 10:497-504, 1995
- [27] Di Iorio BR, Bellizzi V, Bellasi A, et al. Phosphate attenuates the anti-proteinuric effect of very low-protein diet in CKD patients. *Nephrol Dial Transplant* 28:632-640, 2013
- [28] Rhee CM, Ahmadi SF, Kovesdy CP, Kalantar-Zadeh K. Low-protein diet for conservative management of chronic kidney disease: a systematic review and meta-analysis of controlled trials. *J Cachexia Sarcopenia Muscle* 9:235-245, 2018
- [29] Mircescu G, Gârneață L, Stancu SH, Căpușă C. Effects of a supplemented hypoproteic diet in chronic kidney disease. *J Ren Nutr* 17:179-188, 2007