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The Effect of a Nutritional Supplement on Chronic Kidney Disease Patients

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Abstract The objective of this study was to evaluate the effects of UNECE U-LP200 on nutritional status and physical function in chronic kidney disease (CKD) patients. From November, 2010 to March, 2011, 33 participants (17 males and 16 females) with mean age 80.7±10.0 years old were recruited from three nursing homes in New Taipei City, Taiwan. All participants were diagnosed with CKD with blood urea nitrogen (BUN) levels ≧ 20 mg/dL or creatinine (Cr) levels ≧ 1.2mg/dL. The study was divided into three periods: the observation (month 0), intervention (month 1), and follow-up (month 2). During the intervention period, UNECE U-LP 200 was given to participants as a substitute for a snack. Anthropometric measurements, nutritional status, and biochemical measurements were obtained. Body weight and body mass index (BMI), as well as a nutritional indicator, geriatric nutritional risk index (GNRI), all increased after one month of the UNECE U-LP200 intervention ($p < 0.05$). Most of the biochemical measurements were within the normal range, with no significant differenced during the experiment, but plasma fasting blood glucose and triglyceride both improved after one month of the UNECE U-LP200 intervention ($p < 0.05$). The results thus show that UNECE U-LP200 was well-tolerated and could help the participants to maintain a good nutritional status and prevent physical damage.

Keywords: *chronic kidney failure, chronic kidney disease, nutritional supplement, nutritional status, renal*

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1. Introduction

Chronic kidney disease (CKD) has become a worldwide public health issue. Taiwan has a relatively high prevalence and incidence of end-stage renal disease compared to other countries, and thus the proportion of people undergoing dialysis is also high [1,2]. The disproportionate share of healthcare resources and the morbidity and mortality associated with CKD increase the burden to the public health system and decrease patients' quality of life. If further deterioration of renal function could be prevented, the onset of dialysis may be delayed, or even avoided.

Nutrition plays an important part in the management of CKD. The recommended daily protein intake for healthy adults is 0.8-1.2 g/kg. For stable, non-dialysis dependent individuals, a low-protein diet (LPD) is recommended with a daily intake of 0.6-0.8 g/kg with at least 50% of high biological value protein [3,4]. Loss of appetite is highly prevalent in CKD patients, which might cause insufficient dietary intake and result in protein-energy malnutrition. Several studies have reported the beneficial effects of taking a renal-specific supplement on nutritional status and maintenance of renal function, especially in dialysis patients [5-12]. However, few reports specifically investigate the effects of nutritional supplements among pre-dialysis patients. Since it is now clear that CKD alters intestinal flora by uremic toxicity, inflammation, malnutrition and other comorbid conditions, and thus we reason that probiotics may help maintain intestinal microflora [13].

2. Materials and Methods

We investigate the effect of UNECE U-LP200, a novel renal-specific supplement with three common probiotic strains *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Lactococcus lactis* on nutritional status and biochemical parameters.

2.1. Nutritional Supplement for CKD

UNECE U-LP200 is a low protein supplement containing protein, fat, and carbohydrate, each contributing to 8%, 35% and 57% of the total energy intake. The ingredients of UNECE U-LP 200 include whey protein, soybean protein, maltodextrin, maltitol, palatinose, soluble dietary fiber, canola oil powder, sunflower oil powder, medium-chain triglyceride powder, L-carnitine, L-arginine, choline bitartrate, vanilla powder,

guar gum, lactoferrin, calcium citrate, potassium chloride, potassium magnesium, ferric pyrophosphate, sodium citrate, zinc gluconate, D-gluconic acid copper (II) salt, manganese gluconate, yeast selenium, yeast chromium, yeast molybdenum, potassium iodide, vitamin A acetate, vitamin D3, vitamin E acetate, vitamin K1, β-carotene, vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin C, folic acid, biotin, nicotinamide, calcium pantothenate, taurine, and three common probiotic strains: *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Lactococcus lactis*.

2.2. Participants

This clinical trial was approved by the Taipei Medical University-Joint Institutional Review Board, approval no.: 201008004. The study was conducted from November, 2010 to March, 2011. All participants were older than 20 years old, clinically diagnosed as Stage III or stage IV CKD, BUN levels ≧ 20 mg/dL or Cr levels ≧1.2mg/d, in stable condition and receiving appropriate treatment. The exclusion criteria were those individuals with terminal cancer and those who participated in the trial for less than four weeks. Thirty-six patients were initially recruited from three nursing homes in the Banqiao District of the New Taipei City, Taiwan, after signing an informed consent form and the agreement of the attending physician had been obtained. During the study, three patients dropped out because of poor compliance. A total of 33 patients with complete data were thus examined in the analysis, and their baseline characteristics are shown in Table 1.

Table 1. Baseline Characteristics of the Patients

	All	Male	Female
Case (n)	33	17	16
Rate (%)	100	57	43
Age (years)	80.7 ± 10.0	77.9 ± 11.5	83.9 ± 10.7
Body height (cm)	155.5 ± 7.8	160.2 ± 6.1	150.5 ± 4.5
Body weight (kg)	52.7 ± 8.4	55.2 ± 7.0	50.0 ± 4.4
BMI (kg/m^2)	21.9 ± 3.9	21.5 ± 2.8	22.2 ± 2.4
History of comorbidity			
CVA (n)	6	3	3
Hypertension (n)	21	12	9
DM (n)	15	5	10
Dementia (n)	10	5	5
Others(n)	20	11	9

Data are expressed as mean ± SD.
Body height was calculated using the knee length by applying the calculation: for males :85.1 + 1.73* - 0.11*age; for females:91.45 + 1.53* knee length -0.16 *age.
CVA, cerebral vascular accident; DM, *diabetes mellitus*.

2.3. Intervention Study

Anthropometric measurements and blood pressure were taken. The body mass index (BMI) was calculated as weight (kg)/height (m^2), which was used as a reference for calculating the daily energy requirement. During nutritional consultations, the daily energy requirement was calculated by the same clinical dietitian for each participant. The nursing home usually supplied snacks in the afternoon such as one cup of milk (240mL), three cookies, one bowl of oat porridge, one bowl of mung bean soup or fruit, and the calorie and macronutrients of snake was shown as supplement Table 1. In average, UNECE U-LP200 increased 366 to 461 kcal of daily caloric and 0.2 to 2.3 g of dietary fiber intake in the intervention period Fifty-five grams of UNECE U-LP200 dissolved in 250 ml of water, twice a day, was substituted for typical snacks. Another 55g of U-LP200 was provided between the breakfast and lunch. So in total 500 Kcal of U-LP200 was given to the participants.

The study was divided into three periods: month 0 (observation period), in which the participants maintained their usual diet and the dietary records for two consecutive days were taken; month 1 (intervention period), in which 110g of UNECE U-LP200 replaced a 500 Kcal snack from their usual diet; month 2 (follow-up period) , in which the participants stopped taking UNECE U-LP200 and returned to the pre-intervention diet. All blood and urine samples were taken by the Department of Laboratory of Taipei Medical University Hospital after eight hour fasting. Complete blood count and albumin, total protein for nutrition parameters; total cholesterol and triglyceride, low-density-lipoprotein cholesterol (LDL-C) and high-density-lipoprotein cholesterol (HLDL-C) concentrations for lipid profile; blood urea nitrogen and creatinine for renal function; glutamate oxaloacetate transaminase (GOT), glutamic pyruvic transaminase (GPT), γ-glutamyl transpeptidase (γ-GT), total bilirubin (TB), and lactic dehydrogenase for liver function; other measurements: glycated hemoglobin, creatine phosphokinase (CPK) and uric acid, electrolytes: sodium, potassium, chlorine, calcium, magnesium, and phosphorus. Urine tests included analyses of color, appearance, specific gravity, urine urea nitrogen, urine sodium, and urine osmolality. Nutritional assessment, subjective global assessment (SGA) and geriatric nutritional risk index (GNRI) were conducted by the same clinical dietitian for all participants. GNRI is an index, specifically developed for the elderly, with the formula 1.489*serum albumin concentration (g/L)] +[41.7*(current weight/ideal weight)] [14]. SGA is a standardized evaluation form to collect patient's clinical history and anthropometric measurements [15].

2.4. Statistical Analyses

All statistical analyses were performed using the statistics software SAS for Windows 9.01. The paired-t-test was used and considered statistically significant at $p < 0.05$.

3. Results

3.1. Dietary Information

Dietary data showed that during intervention the energy intake was increased by 181.2 ± 51.9 Kcal. Protein, carbohydrate, and dietary fiber was increased by 3.4±2.3 g, 24.6±11.7 g and 1.5±0.9 g, respectively. No significant difference in energy and macronutrients intake was found between baseline and follow-up period.

3.2. Anthropometric Measurements

At the end of the intervention period (month 1), the average body weight increased from 52.7 ± 8.4 kg to 53.8

± 7.7 kg, compared to the observation period (month 0). The BMI increased from 21.9 ± 3.9 kg/m2 to 22.9 ± 3.9 kg/m2 (Table 2).

3.2. Geriatric Nutritional Risk Index (GNRI) and Subjective Goal Assessment (SGA)

The GNRI increased from 96.1 ± 9.3 (month 0) to 98.0 ± 7.3 (month 1) ($p < 0.05$). SGA did not change during the study period (Table 2).

Table 2. Anthropometric and Nutritional Assessments.

	Month 0	Month 1	Month 2
BW (kg)	52.7 ± 8.4	53.8 ± 8.7†	56.1 ± 8.5‡
BMI (kg/m^2)	21.9 ± 3.9	22.3 ± 3.9†	23.7 ± 4.0‡
SBP (mm/Hg)	125.7 ± 17.6	125.9 ± 19.0	127.7 ± 14.9
DBP (mm/Hg)	70.7 ± 7.0	69.7 ± 8.7	72.1 ± 9.4
Defecation status (times/day)	0.7 ± 0.4	0.7 ± 0.4	0.6 ± 0.4
GNRI	96.1 ± 9.3	98.0 ± 7.3	98.2 ± 7.6a‡
SGA	5.8 ± 1.0	6.1 ± 0.7	5.9 ± 1.0

Data are expressed as mean ± SD.
† paired t-test shows the comparison between month 1 and month 0. p < 0.05;‡ paired t-test shows the comparison between month 2 and month 0.
Abbreviations: BW, body weight; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure, GNRI, geriatric nutritional risk index; SGA, subjective goal assessment

3.3. Biochemical Measurements

All biochemical results are shown in Table 3. Fasting blood glucose levels decreased from 131.6 ± 83.7 mg/dL (month 0) to 112.6 ± 50.5 mg/dL (month 1) ($p < 0.05$). Triglyceride concentrations also showed a decrease from 128.0 ± 0.4 mg/dL to 101.3 ± 52.0 mg/dL ($p < 0.05$). There were ssignificant increases in the concentrations of CPK (66.0 ± 35.4 mg/dL to 90.2 ± 65.8 mg/dL, $p < 0.05$), GOT (22.6 ± 13.3IU/L to 27.4 ± 14.4IU/L, $p < 0.05$), GPT (15.8 ± 10.1 IU/L to 24.3 ± 19.3IU/L, $p < 0.05$) and TB (0.3 ± 0.1mg/dL to 0.4 ± 0.2mg/dL, $p < 0.05$), potassium (4.4 ± 0. 8mEq/dL to 4.9 ± 1.0 mEq/dL, $p < 0.05$); magnesium (2.2 ± 0.2 to 2.3 ± 0.3mg/dL, $p < 0.05$) was within the normal range (Table 3). There were no significant differences in other measurements (Table 4). The urine analysis showed normal results (Table 5).

Table 3. Biochemical Measurements

	Normal range		Month 0	Month 1	Month 2
Alb	3.5-5.2	g/dL	3.7 ± 0.4	3.7 ± 0.5	3.7 ± 0.4
TP	6.6-8.7	g/dL	6.8 ± 0.6	6.8 ± 0.6	6.7 ± 0.7
BUN	6-20	mg/dL	23.0 ± 7.2	24.0 ± 11.8	24.6 ± 9.7
Cr	0.5-1.2	mg/dL	1.3 ± 0.4	1.3 ± 0.6	1.3 ± 0.5
UA	2.5-7.0	mg/dL	5.9 ± 2.1	6.3 ± 2.4	6.1 ± 1.8§
TC	<200	mg/dL	161.0 ± 30.5	160.3 ± 40.1	156.8 ± 37.1
TG	<200	mg/dL	128.0 ± 88.5	101.3 ± 52.0†	108.1 ± 55.3
LDH	35-225	IU/L	201.0 ± 75.2	195.3 ± 54.3	216.2 ± 121.1
CPK	38-174	IU/L	66.0 ± 35.4	90.2 ± 65.8†	84.9 ± 60.3‡
γ-GT	10-66	IU/L	30.9 ± 41.3	33.6 ± 51.1	38.4 ± 54.2
TB	0.0-1.0	mg/dL	0.3 ± 0.1	0.4 ± 0.2†	0.4 ± 0.3
GOT	<37	IU/L	22.6 ± 13.3	27.4 ± 14.4	25.5 ± 12.5
GPT	<41	IU/L	15.8 ± 10.1	24.3 ± 19.3†	20.5 ± 11.6‡
AC	70-100	mg/dL	131.6 ± 83.7	112.6 ± 50.5†	126.2 ± 62.3
HbA1c	4.0-6.0	%	6.7 ± 1.6	6.6 ± 1.8	6.7 ± 1.9
Cl	98-107	mEq/dL	102.2 ± 4.3	103.1 ± 5.4	103.5 ± 5.9
Na	136-145	mEq/dL	137.9 ± 4.0	137.9 ± 4.4	138.1 ± 4.8
K	3.5-5.1	mEq/dL	4.4 ± 0.8	4.9 ± 1.0†	5.2 ± 1.2‡
Ca	8.6-10.2	mg/dL	8.5 ± 0.4	8.4 ± 0.8	8.0 ± 1.2‡
P	2.7-4.5	mg/dL	3.4 ± 0.8	3.5 ± 0.7	3.4 ± 0.7
Mg	1.8-2.3	mg/dL	2.2 ± 0.2	2.3 ± 0.3†	2.2 ± 0.4§

Data are expressed as mean ± SD.
†paired t-test shows the comparison between month 1 and month 0; ‡ paired t-test shows the comparison between month 2 and month 0; §paired t-test shows the comparison between month 2 and month 1.
Abbreviations: Alb, albumin; TP, total protein; BUN, blood nitrogen urea; Cr, creatinine; UA, uric acid; TC, total cholesterol; TG, triacylglycerol; LDH, lactic dehydrogenase; CPK, creatine phosphokinase; γ-GT, γ-glutamyl transpeptidase; TB, total bilirubin; GOT, glutamate oxaloacetate transaminase; GPT, glutamic pyruvic transaminase; AC, before meal; HbA1c, glycated hemoglobin; Cl, chloride; Na, sodium; K, potassium; Ca, calcium; P, phosphorus; Mg, magnesium.

Table 4. Complete Blood Count

	normal range (unit)		month 0	month 1	month 2
WBC	4.0-11.0	10^3 /μL	7.6 ± 2.4	8.0 ± 4.1	7.8 ± 3.2
RBC	4.2-6.1	10^6/μL	4.0 ± 0.8	3.8 ± 0.7	3.9 ± 0.7
Hb	12-18	g/dL	11.5 ± 1.7	12.3 ± 1.9	11.7 ± 1.8
Ht	37-52	%	34.5 ± 5.1	33.9 ± 5.7	34.8 ± 5.4
MCV	80-99	fL	88.8 ± 5.4	89.5 ± 7.2	88.3 ± 7.1‡§
MPV	7.2-11.1	fL	10.2 ± 1.0	10.4 ± 0.9	10.3 ± 1.0
MCH	26-34	pg	29.6 ± 3.0	29.8 ± 2.6	29.9 ± 9.4
MCHC	33-37	g/dL	33.4 ± 0.7	33.2 ± 1.2	33.9 ± 0.9§
PLT	130-400	10^3/μL	230.7 ± 72.1	232.6 ± 73.0	229.2 ± 63.4
RDW-CV	11.5-14.5	%	14.1 ± 1.1	14.1 ± 1.2	13.7 ± 0.9‡§
RDW-SD	-	%	45.4 ± 5.6	45.9 ± 5.3	43.8 ± 3.8§
PDW	-	%	11.7 ± 2.1	12.2 ± 1.8†	12.2 ± 2.1

Data are expressed as mean ± SD.
†paired t-test shows the comparison between month 1 and month 0; ‡ paired t-test shows the comparison between month 2 and month 0; §paired t-test shows the comparison between month 2 and month 1.
Abbreviations: WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume.

Table 5. Urine test results

	normal range	month 0	month 1	month 2
UUN random	-	378.8±210.1	373.5±163.5	368.9 ±183.3
Urine Na	-	79.9±34.5	83.8±34.2	73.7 ±28.9
Osmolarity	50-1200 mOsm/kg	377.3±131.9	377.2±146.1	349.1 ±130.6
SP.Gr	1.003-1.030	1.0 ±0.0	1.0±0.0	1.0 ±0.0
pH	4.5-8.0	7.2 ±1.3	7.5±1.0	7.5 ±12.0
Urobilinogen	0.1-1.0 E.U/dl	0.1 ±0.0	0.1±0.0	0.1 ±0.0
Protein	-	-	-	-
Sugar	-	-	-	-
Ketone	-	-	-	-
Bilirubin	-	-	-	-
Nitrite	-	-	-	-
WBC	-	-	-	-
Color	yellow	yellow	yellow	yellow

Data are expressed as mean ± SD. Abbreviations: UUN, Urinary Urea Nitrogen; Na, sodium; SP.Gr, Specific gravity; WBC, white blood cell count.

4. Discussion

UNECE U-LP200 is a low-protein oral supplement, specifically formulated for patients with chronic kidney failure. The participants received 500Kcal of UNECE U-LP200 to replace two snacks from their original diets. During the study period, the participants displayed no intestinal symptoms, such as diarrhea or bloating, and no change in defecation status (0.7 times/day), indicating good enteral tolerance to UNECE U-LP200.

Nutritional status is generally evaluated by the clinicians using anthropometric and biochemical measurements, as well as SGA. Caglar et al. (2002) reported that a renal-specific supplement given during dialysis for six months significantly improved serum albumin and prealbumin levels and SGA, but not BMI [6]. Fouque et al (2008) reported that daily supplement of a renal specific supplement for three months in hemodialysis patients did not result in significant increases albumin and prealbumin levels, but did cause improvements in SGA and quality of life (QOL) score [7]. In this present study, the BMI increased significantly after one month of supplementation. This increase also resulted in an improved GNRI score trend, although this was not significant. GNRI is an index for assessing the risk of malnutrition in the elderly population. The higher the GNRI value, the lower the risk. According to a study by Bouillanne et al. (2005), GNRI < 82, GNRI 82 to < 92, GNRI 92 to ≦ 98, and GNRI > 98 are classified as high, moderate, low, and no risk of malnutrition. After a month of intervention, the mean GNRI was improved from the low risk to no risk group. No significant increase was found for SGA. As in Fouque et al. (2008) [7], no significant improvements in serum albumin levels were observed. This is likely due to the short supplementation period of one month, compared to six months in Caglar et al. (2002) [6]. It has been stressed that multiple nutritional indicators should be used for such analyses, as, for example, lower albumin levels are associated with inflammation.

It is also important to evaluate biochemical measurements other than the ones which are related to "nutritional status." Since many CKD patients also have other superimposed conditions, such as cardiovascular diseases, diabetes mellitus, hypertension and dyslipidemia, nutritional interventions should not generate additional burdens to these pre-existing conditions. In the present study, no adverse effects on the hepatic system and no deterioration to the renal system were observed, indicating that U-LP200 is generally safe for CKD patients.

Biochemical measurements frequently fluctuate in response to the individual's physiology and environmental factors. The biochemical measurements obtained in this study showed decreased levels of blood glucose and triglycerides. This may be attributed to the use of soy protein as the main protein source, as well as dietary fiber and prebiotics, which have been clinically proven to reduce cholesterol or triglyceride levels in patients with hyperlipidemia and hypercholesterolemia [16,17]. In addition, dietary fiber is also effective in lowering fasting blood glucose levels [18].

This study only followed up the participants at one month interval. The short follow-up period was the limitation in this study, and may explain the lack of significant difference between month 1 and month 2. Villareal et al (2006) reported that elderly participants only lost 3% of body weight after four weeks of dietary intervention which decreased 750 Kcal daily energy intake [19]. In another study also by Villareal et al (2011), after four weeks of reducing 500 Kcal daily intake plus exercise intervention, elderly participants had only reduced 2% of their body weight [20]. In this study, shorter follow-up period and less different energy intake (average of 181 Kcal) may contribute to the non-significant difference in BMI and GNRI.

The UNECE U-LP200 supplement differs from other, similar supplements on the market in that probiotics are added to the formula. Chronic kidney disease affects intestinal microflora in many respects. Uremia can impair the intestinal barrier function and change the biochemical milieu of the intestinal tract, which can initiate proinflammatory reactions and disrupt the resident microflora composition. Three common lactic acid prebiotics were thus added to the supplement. However, we did not assess the effects of adding probiotics on the microflora composition. Modulation of the microflora and

more significant improvements in nutritional status, including albumin and prealbumin levels, may be observed in future studies in which the supplement is given to patients for a longer period (six months or more).

5. Conclusions

UNECE U-LP200 is a low-protein oral supplement, specifically formulated for patients with chronic kidney failure. In this study, we showed that UNECE U-LP200 was well tolerated by CKD patients, and their nutritional status could be maintained. Further studies should examine the nutritional effects of U-LP200 for a longer supplementation period.

Statement of Competing Interests

UNECE U-LP200 was provided by New Bellus Enterprises Co., Ltd. One of the authors, Alice Lan, was an employee of New Bellus Enterprises Co., Ltd., at the time of writing this paper.

List of Abbreviations

CKD, chronic kidney disease
BUN, blood urea nitrogen
Cr, creatinine
BMI, body mass index
GNRI, geriatric nutritional risk index
GOT, glutamate oxaloacetate transaminase
GPT, glutamic pyruvic transaminase
γ-GT, γ-glutamyl transpeptidase
TB, total bilirubin
CPK, creatine phosphokinase
SGA, subjective global assessment
QOL, quality of life.

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Supplemental information

Supplement Table 1. Nutrition information of U-LP200 versus typical snacks

	unit	Calories (Kcal)	Protein (g)	Carbohydrate (g)	Fat (g)	Dietary fiber (g)
U-LP200	55g	250.0	5.2	36.0	9.8	2.3
Milk	240cc	134.1	7.0	9.8	7.5	0.0
Crackers	12g	60.9	0.9	7.7	3.0	0.3
Porridge	15g oat 10g sugar	99.4	1.8	20	1.4	1.6
Green bean soup	10g green bean 20g sugar	111.4	2.3	26.1	0.1	1.6
Banana	125g	106.2	1.8	27.6	0.1	2.0
Papaya	100g	38.5	0.5	0.1	10.1	1.3