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Study of Dietary Supplement with Compound Proteins on the Improvement of Nutrition of Dialysis Patients

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Abstract: The study aims to investigate the effect of a liquid supplement UNECE U-99 on the nutritional status of patients receiving maintenance dialysis. For this purpose, 47 participants (27 males and 20 females), aged 29 to 82 (average: 60), who underwent maintenance dialysis were recruited to the study. Two participants were excluded from the analysis as one was unwell for the study and the other was transferred to another hospital. Remaining 45 participants (25 males and 20 females) to be included in the final analysis. The participants were given 4 weeks of UNECE U-99 supplementation. The nutritional evaluation, biochemical tests and anti-oxidant capacity measurements were performed before and after the intervention. After 4 weeks of UNECE U-99, dietary energy intake and uptake of protein, fat and carbohydrate were significantly increased. Plasma albumin levels were elevated ($p<0.01$). A significant increase in anti-oxidant capacity was also observed. Calcium levels were increased ($p<0.05$) whereas potassium levels were reduced ($p<0.01$). Post-dialysis creatinine levels at week 4 compared to the baseline were decreased ($p<0.01$) and uric acid levels at week 4 were also reduced. It is concluded that UNECE U-99, a nutritional supplement designed for dialysis patients improved their nutritional status in this short term study.

Key words: Chronic renal failure, chronic renal disease, dialysis, nutritional supplement

INTRODUCTION

Patients with an end stage renal disease usually undergo dialysis. Dialysis removes toxins from the blood but in the meantime the loss of nutrients is also common. Restricted protein intake in the dietary aspect of the disease management is recommended. Protein contributes a major proportion of the daily calorie intake. Many patients on maintenance dialysis have the protein energy wasting (PEW) condition. PEW is a risk factor for poor quality of life, increased mortality and morbidity in dialysis patients (Fouque *et al*., 2007). Approximately 1/10 of dialysis patients are severely malnourished. Factors contributing to either PEW or malnutrition include reduced energy and protein intake and catabolic stimulus of dialysis. Deficiencies in vitamin B_6, vitamin C, folic acid, calcium, iron and zinc have also been found (Kopple, 1999). Nutritional supplementation has been shown to be effective in improving nutritional status in patients on maintenance dialysis (Fouque *et al*., 2008; Galland *et al*., 2001; Sezer *et al*., 2014). In these studies, serum albumin levels have been used as major clinical outcome for the biochemistry marker of the nutritional status and malnutrition has also been defined as the albumin concentration <3.8 g/dl (Fouque *et al*., 2007).

It has been suggested that oxidative stress plays an important role in the renal disease. The increased oxidative stress occurs where a preferential shift towards the pro-oxidative capacity than anti-oxidative capacity (Locatelli *et al*., 2003). Malnutrition, chronic inflammation and age, common in ESRD patients, are major contributing factors to increased oxidative stress (Locatelli *et al*., 2003). In ESRD patients, cardiovascular diseases are overly represented as these diseases can also be attributed to increased oxidative stress (Locatelli *et al*., 1999). High levels of oxidized low density lipoprotein (oxLDL), which is formed in a highly oxidative environment, contribute to plaque formation in the blood vessels in atherosclerosis. Several strategies such as supplementation of N-acetylcysteine (NAC), vitamin C and the use of vitamin E coated dialysis membrane have demonstrated beneficial nutritional and antioxidant outcomes (Feldman *et al*., 2012; Giray *et al*., 2003; Huang *et al*., 2015; Lines *et al*., 2014; Zhang *et al*., 2013).

Kalantar-Zadeh and coworkers were first to report that commercially available nutritional supplement was well-tolerated and increased serum albumin levels in hypoalbuminemic hemodialysis patients (Kalantar-Zadeh *et al*., 2005). However, no direct assessment on

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the antioxidant activity was reported. It is interesting to know that in addition to improvement on the nutritional status whether antioxidant status can be enhanced. In the present study, we investigated that the effect of a commercially available renal supplement on the nutritional and anti-oxidant status in patients undergoing maintenance dialysis.

MATERIALS AND METHODS

Study participants: The study was approved by the Institutional Review Board of Chung Shan Medical University Hospital. 47 participants aged 29-82, including 27 males, 20 females were recruited. However during the 4-week study, one participant had a health issue and the other was transferred to another hospital. This left a study sample of n = 45 (25 males and 20 females). Among the participants, 3 individuals received peritoneal dialysis. The remaining participants received hemodialysis and of these patients, 5 individuals received electrolyte hemodialysis. 17 out 45 participants had diabetic nephropathy. The study was conducted from 1st of July, 2007 to 31st of December, 2007.

Procedures: Participants were given nutritional consultations and required daily energy intake was calculated. The amount of UNECE U-99 given to participants was individually determined in order to keep their total energy intake constant over the intervention period. Generally, participants were given one to two packets of UNECE U-99/day. Each packet is 57 g (290 Kcal) and contains 17.1% (12.4 g) of protein, 47.2% (15.2 g) of fat and 35.6% of carbohydrate (25.8 gm). UNECE U-99 was either consumed as part of the meal or as snack.

Anthropometric and biochemical measurements were recorded before and after the 4-week intervention. Additionally, dietary evaluation and clinical assessments were also given. The measurements include.

Anthropometric measurements: Midarm circumference (MAC), midarm muscle circumference (MAMC), triceps skin fold (TSF) and waist and hip circumferences. Weight and height were used to calculate Body Mass Index (BMI) (weight/height in kg/m^2). The waist to hip ratio (WHR) was then calculated (waist circumference/hip circumference). The same researcher took WHR and TSF measurements to minimize the variability. Systolic and diastolic blood pressures were also measured.

Estimated energy requirement: The energy requirement was calculated by the daily activity level, respiratory quotient (RQ) and basal metabolism rate.

Biochemical measurements: Blood was sampled after an overnight fast. These included plasma levels of albumin, prealbumin, blood glucose, blood urine nitrogen, plasma lipids, hemoglobin, uric acid, creatinine, iron, calcium, sodium, potassium, magnesium, phosphorus and hepatic function measurements including glutamate oxaloacetate transaminase (GOT) and glutamic pyruvic transaminase (GPT). Whole blood cell count including red blood cells (RBC), white blood cell (WBC) and platelet numbers was also performed.

Clinical symptoms: Any discomforts including nausea, vomiting, diarrhea or constipation were recorded. Clinical examination for other symptoms or change in wound size was taken.

Nutritional/dietary evaluation: Average daily energy intake was calculated based on participants' 24 h recall and compared to the basal energy expenditure (BEE), which was calculated using the Harris-Benedict Equation.

Measurements for superoxide concentration and whole blood anti-oxidant capacity: Total anti-oxidant capacity was measured using the trolox equivalent antioxidant capacity (TEAC) method. Superoxide (free radicals) levels in whole blood were measured using the chemiluminescence method and lucigenin amplification.

Statistical analysis: Statistical analysis was conducted using the SPSS statistics software. The results are expressed as mean±SD. Results were compared using paired t-test and considered statistically significant if $p<0.05$.

RESULTS

Participant characteristics: At the entry into the study, participants completed questionnaires and their clinical records were assessed to select eligible individuals. After selection, 47 participants met criteria and valid consents were obtained. Two participants left the study as one was unwell and the other was transferred to another hospital. Therefore, the remaining 45 participants completed the study and reported no discomforts during 4 weeks of intervention.

Effect of UNECE U-99 on anthropometric measurements: BMI and WHR were calculated at the baseline and at week 4 (Table 1). At week 0 (baseline), the mean of weight, BMI and WHR 57.02±8.82 (kg), B22.06±3.16 (kg/m^2), B0.88±0.06 (W/H), respectively. After the 4-week intervention, no significant change in these measurements was found. Similarly, there was no change in TSF, MAC and MAMC at the end of intervention compared to the baseline (Table 2).

Table 1: Change in weight, BMI and WHR

(n = 45)	Week 0	Week 4
Weight (kg)	57.02±8.82	57.22±8.44
BMI (kg/m^2)	22.06±3.16	22.26±2.88
WHR (W/H)	0.88±0.06	0.89±0.05

Data are expressed as mean±SD

Table 2: Change in TSF, MAC and MAMC

	Week 0	Week 4
TSF (mm)	17.78±7.41	17.80±6.84
MAC (cm)	25.64±2.60	25.63±2.63
MAMC (cm)	20.48±3.01	20.32±2.87

Data are expressed as mean±SD

Table 3: Total antioxidant capacity measured by the TEAC method

	Pre-dialysis	Post-dialysis
	---------- TEAC (mM) ----------	
Week 0	0.70±0.07	0.69±0.07
Week 4	0.88±0.07**	0.84±0.06**

Data are expressed as mean±SD. **p<0.01 week 0 vs. week 4

Table 4: Superoxide concentration

	Pre-dialysis	Post-dialysis
	---------- Counts/10 sec ----------	
Week 0	27380.25±36506.48	29795.20±89639.74
Week 4	17640.02±15459.44*	12594.73±12278.10

Data are expressed as mean±SD
*p<0.05 week 0 vs. week 4

Effect of UNECE U-99 on and anti-oxidant capacity and free radical levels: The total anti-oxidant capacity of the plasma was measured by the TEAC method. There was an increase on the pre-dialysis level of TEAC (0.88±0.07 mM) at week 4 compared to the baseline (0.70±0.07 mM) (p<0.01). Similarly, a statistically significant increase in post-dialysis TEAC levels was observed from 0.69±0.07 mM at the baseline to 0.84±0.06 mM at week 4 (p<0.01). The results are described in Table 3.

The pre-dialysis amounts of superoxide in the blood were also reduced at week 4 (17640.02±15459.44 counts/10 sec) vs. at the baseline (27380.25±36506.48 counts/10 sec) (p<0.05). There were also reduced post-dialysis levels (Baseline: 29795.20±89639.74 counts/10 sec vs. week 4: 12594.73±12278.10 counts/10 sec) but did not reach statistical significance. The results are shown in Table 4.

Effect of UNECE U-99 on biochemical measurements: The results of biochemical measurements are described in Table 5. Mean serum albumin level was increased from 3.85±0.32 mg/dL at the baseline to 4.06±0.34 mg/dL after the 4-week intervention (p<0.01), however no change in prealbumin levels was observed. Mean serum cholesterol level was lower at the end of intervention (156.89±29.52 mg/dL) compared to 164.76±28.86 mg/dL at the baseline (p<0.05).

No change was observed for triglyceride, blood glucose and blood urine nitrogen. There was no significant change in the pre-dialysis creatinine level, but the post-dialysis creatinine level was reduced from 3.54±1.08 mg/dL at the baseline to 3.24±0.98 mg/dL at the end of week 4. The uric acid level was significantly reduced after 4 weeks (p<0.01). At the end of week 4, calcium concentration had an increase from 9.42±0.76 to 9.63±0.75 mg/dL (p<0.05) whereas potassium concentration had a decrease from 4.36±0.84 to 3.98±0.73 mEq/L (p<0.01). No significant differences were observed for other measurements. The results are summarized in Table 5.

No significant change for other biochemical measurements including sodium, phosphorus, hemoglobin, GOT, GPT, RBC, WBC and platelet was found.

Harris-Benedict Equation was applied to calculate the basal energy expenditure (BEE), which was compared to the actual daily energy intake according to the 24 h recall by the participant. The results are depicted in Table 6. 4 week's UNECE U99 supplementation, the BEE was increased from 1796.11±204.36 Kcal at the base line to 1828.84±218.1 Kcal at week 4 (p<0.05). The daily energy intake after intervention was significantly improved to 1831.83±227.87 Kcal, compared to 1474.66±300.20 Kcal at the baseline (p<0.05). The results are summarized in Table 6.

Effect of UNECE U-99 on nutrient intake: Diet records were examined before and after 4 weeks of intervention. Daily intake for protein, fat and carbohydrate before the intervention were 42.25±12.54 g (13.12%), 45.84±22.62 g (31.29%) and 177.14±57.34 g (55.58%), respectively. A significantly increased intake of amounts in all three nutrients was observed (p<0.01) (Table 7).

Before the intervention, 28 participants had constipation, but only 17 participants reported symptoms of constipation. There were 18 people with loss of appetite at the beginning of the study; however half of participants reported increased appetite. Fatigue was only reported in 25 of 35 participants after the 4-week supplementation (Table 8).

DISCUSSION

UNECE U-99 is a nutritional supplement, specifically formulated for patients who suffer from acute or chronic kidney failure and require dialysis. The loss of nutrients is prominent during the dialysis process, hence maintaining the nutritional status is particularly important for their long-term health. In this study, 45 participants who underwent dialysis were given a 4-week supplementation of UNECE U-99. No adverse effects were reported.

The effect of UNECE U-99 supplement was evaluated by following indicators: anthropometry, energy requirement analysis, biochemical measurements. Our results showed that both BBE and the actual daily energy intake improved significantly after 4 week of UNECE U-99 supplementation. The recommended daily intake for

Table 5: Comparison of biochemical measurements at the baseline and after 4-week's intervention

Biochemical's	Week 0	Week 4
Albumin (mg/dL)	3.85±0.32	4.06±0.34**
Prealbumin (mg/dL)	33.59±11.04	33.54±9.24
Cholesterol (mg/dL)	164.76±28.86	156.89±29.52*
Triglyceride (mg/dL)	150.73±80.77	134.44±76.43
Blood glucose (mg/mL)	114.31±44.35	107.98±35.37
Pre-dialysis BUN (mg/dL)	62.07±19.60	63.63±17.08
Post-dialysis BUN (mg/dL)	17.35±8.34	16.51±6.01
Pre-dialysis creatinine (mg/dL)	9.99±2.04	9.95±1.78
Post-dialysis creatinine (mg/dL)	3.54±1.08	3.24±0.98*
Uric acid (mg/dL)	7.01±1.41	6.42±1.51**
Calcium; Ca (mg/dL)	9.42±0.76	9.63±0.75*
Sodium; Na (mEq/L)	138.80±6.52	138.27±3.12
Potassium; K (mEq/L)	4.36±0.84	3.98±0.73**
Phosphorus (mg/dL)	4.69±1.55	4.43±1.13
GOT (U/L)	17.47±4.67	16.93±4.17
GPT (U/L)	12.67±6.33	12.53±5.72
RBC (gm% H)	360.71±55.16	361.89±61.60
WBC (10^4/mm^3)	6062.02±2038.96	6180.00±1863.97
Platelet (% H)	188422.22±71804.18	195844.44±61415.85
Hemoglobin; Hb (g/dL)	10.47±1.09	10.50±1.47
Data are expressed as mean±SD	*p<0.05 week 0 vs. week 4	**p<0.01 week 0 vs. week 4

Table 6: BBE and daily energy intake values

	Week 0	Week 4
BEE (Kcal/day)	1796.11±204.36	1828.84±218.15*
Daily energy intake (Kcal/day)	1474.66±300.20	1831.83±227.87*
Data are expressed as mean±SD	*p<0.05 week 0 vs. week 4	

Table 7: Comparison of nutrient intake

	Week 0	Week 4
Protein (gm)	42.25±12.54 (13.12%)	55.98±10.55 (13.61%)**
Fat (gm)	45.84±22.62 (31.29%)	63.56±20.03 (34.75%)**
Carbohydrate (gm)	177.14±57.34 (55.58%)	214.04±57.00 (51.73%)**

Data are expressed as mean±SD. **p<0.01 week 0 vs. week 4

Table 8: Frequency of clinical symptoms

	Week 0	Week 4
Constipation	28	17
Loss of appetite	18	9
Fatigue	35	25

patients on dialysis is 35 kcal/kg/day in order to meet the nutritional needs. Prior to UNECE U-99 supplementation, the daily energy intake for participants was 25 kcal/kg/day whereas after the intervention it was increased to 32 kcal/kg/day, achieving approximately 91% of the recommended intake. As a result, the consumption of protein, fat and carbohydrate were significantly increased. Importantly, sufficient intake of protein is vital and recommended daily amount is 1.2-1.5 g/kg/day. Before the UNECE U-99 intervention, the protein intake was 1.0 g/kg/day. After 4 weeks, the mean protein intake was increased to 1.2 g/kg/day, achieving the recommended intake.

Albumin levels have been used as an indicator for nutritional status for patients on maintenance dialysis (Chen *et al*., 1999). After 4 weeks of UNECE U-99 supplementation, plasma albumin was significantly increased. The total energy and protein intake were significantly improved. UNECE U-99 contains high quality whey protein, which quickly enters the gastrointestinal tract to be absorbed (Marshall, 2004). These two factors may contribute to the increase in the serum albumin level.

Plasma cholesterol level was significantly reduced after 4 weeks. This may be attributed to soybean protein and patented dietary fiber in UNECE U-99, which have been clinically proven to reduce cholesterol levels in dialysis patients with hyperlipidemia and hypercholesterolemia (Erdman and Committee, 2000; Reynolds *et al*., 2006). Lowering cholesterol level is beneficial to dialysis patient as one of the major comorbidity of ESRD patient is cardiovascular diseases and elevated cholesterol levels are risks factors for CVD.

4-week's UNECE-U-99 supplementation was able to reduce pre-dialysis concentration of free radicals, such as superoxides. No significant difference was found in post-dialysis concentration. However, at week 4, both pre-and post-dialysis anti-oxidant capacity was enhanced compared to the baseline and at week 4 there

was no further change in anti-oxidant capacity for before and after dialysis. Previous studies showed that whey protein supplementation can effectively enhance glutathione concentration, which scavenge free radicals either directly or enzymatically via glutathione peroxidase to reduce oxidative stress (De Aguilar-Nascimento *et al*., 2011).

Consumption of the supplement was well-tolerated. Moreover, the improvements on symptoms including constipation, loss of appetite and fatigue were also reported by participants (Locatelli *et al*., 2002). UNECE U-99 contains soybean protein and patented dietary fiber, both of which can assist in relieving these symptoms. Nevertheless, the enteral absorption rate varies from individual to individual. A greater proportion of patients may experience such improvements if the intervention period is extended.

Conclusion: UNECE U-99 is well tolerated by patients on dialysis. We provide evidence for the improvements in the nutritional status and dietary intake after a short term supplementation. Moreover, the antioxidant capacity was also enhanced.

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