

The effect of ONCE Renal on minerals and electrolytes in predialysis patients with chronic kidney disease

Bancha Satirapoj¹
Janjira Prapakorn²
Dollapas Punpanich²
Chantima Pongsuparbchon³
Ouppatham Supasyndh¹

¹Division of Nephrology, Department of Medicine, ²Research Unit, Department of Medicine, ³Clinical Research Center, Phramongkutklao Hospital, Phramongkutklao College of Medicine, Bangkok, Thailand

Background: Malnutrition is one common adverse consequence in patients with advanced chronic kidney disease (CKD), and most patients have a lower-than-normal dietary energy intake. The present study was undertaken to examine whether orally administered ONCE Renal formula (ORF) supplement would improve energy intake without minerals and electrolytes disturbances in predialysis patients with CKD.

Methods: All eligible nondiabetic patients with CKD received ORF supplement for 1 week. Nutrition markers, renal function, and minerals and electrolytes were evaluated before and after supplementing. All patients kept a 3-day food record and were interviewed by a registered dietitian.

Results: A total of 29 patients with mean age 64.9 ± 13.3 years were included. Mean estimated glomerular filtration rate was 37.7 ± 12.1 mL/min/1.73 m². A significant increase was observed in amount of energy, fat, fiber, calcium, and magnesium intake after 1 week of ORF supplement. Moreover, in comparison with baseline values, the patients displayed decreased dietary protein intake and blood urea nitrogen and increased serum magnesium. However, no significant change was found in renal function, nutritional markers (body weight, prealbumin, albumin, and protein equivalence of total nitrogen appearance), serum calcium, phosphorus, sodium, potassium, and bicarbonate.

Conclusion: In patients with CKD, ingestion of ORF was well tolerated and had a positive effect with an increase in dietary energy, fat, and fiber intake, as well as a decreased dietary protein intake. No mineral or electrolyte abnormalities were observed during the study.

Keywords: oral-specific renal nutrition, malnutrition, chronic kidney disease

Background

Protein energy wasting (PEW) and inflammation are common adverse consequences of advanced chronic kidney disease (CKD) and are associated with impaired quality of life and increased morbidity and mortality.¹ Several studies have indicated a prevalence of this condition ranging from 20% to 30% and increasing in line with CKD progression.²⁻⁴ In contrast, advanced CKD patients often intake excessive amounts of various nutrients, including protein, sodium, phosphorus, and potassium, that have been associated with increased uremic complications and mortality. These problems can be limited by carefully controlling the composition of the dietary intake.⁵ Therefore, oral-specific renal nutritional supplementation might be one therapeutic intervention for these patients. Therapies designed to increase energy and fiber intake without protein loading and electrolyte disturbances in CKD patients might, therefore, be expected to improve their quality of life, and possibly their survival.

Correspondence: Bancha Satirapoj
Division of Nephrology, Department of Medicine, Phramongkutklao Hospital and College of Medicine, 315 Rajavithi Road, Bangkok 10400, Thailand
Tel/fax +66 2 644 4676
Email satirapoj@yahoo.com

CKD is becoming more common due to the rising incidence of diabetes, hypertension, and obesity.⁶ Optimal predialysis CKD management can improve morbidity, mortality, dialysis, and transplantation outcome.⁷ Applying the various dietary interventions to achieve therapeutic goals in a CKD population would have a beneficial effect on outcomes, including the slowing of the progression of CKD and the treatment of protein energy wasting.⁵ The implementation of dietary interventions can be challenging to the health care team and patients. Most advanced CKD and hemodialysis patients have a lower-than-normal dietary energy intake, and oral nutrition supplements are further needed to achieve intake recommendations.^{8,9} Currently, no consensus guidelines exist on the type, time of initiation, or duration of oral nutrition supplements.¹⁰ The present study was undertaken to examine whether orally administered dietary renal-specific formula or ONCE Renal formula (ORF: Thai Otsuka Pharmaceutical Co., Ltd., Bangrak, Thailand) supplement that provides more energy, fiber, and trace elements intake, and less protein intake could improve energy intake and maintain nutrition status and electrolyte balance among CKD patients. The purpose of the present study was to assess the impact of an ORF supplement on the nutritional status and minerals and electrolytes of predialysis CKD patients.

Methods

This trial was a prospective interventional study in patients with CKD stage III–IV. This study was approved by the Institution Review Board, Royal Thai Army Medical Department, and all subjects participated in the study after giving informed consent. Inclusion criteria of the study included age 18 years or older with CKD stage III or IV, stable renal function or <10% change in glomerular filtration rate (GFR) within 3 months, and no change in any medical treatment within 3 months before starting the study. Exclusion criteria included diabetes mellitus, active malignancy, severe heart, lung, or liver disease, stroke, chronic infection within 1 year of starting the study, and malnourished conditions defined as a loss of $\geq 5\%$ body weight over the past 3 months and serum albumin concentration <3.5 g/dL.

All patients were assigned to ingest ORF for 1 week. The intervention consisted of an orally liquid ORF supplementation instead of 30% of daily total caloric intake of CKD patients. Each serving of ORF preparation consisted of 360 kcal per 76 g and the following ingredients: 7.19 g of proteins, 48.25 g of carbohydrate with fiber 2.99 g, 15.95 g of fat, 143.6 mg of calcium, 143.6 mg of phosphorus, 197.4 mg

Table 1 ONCE Renal formula

| Macronutrient | One serving or 76 g (360 kcal) |
|---|--------------------------------|
| Caloric distribution of macronutrients (%) | |
| Protein | 8% |
| Carbohydrate | 52% |
| Fat | 40% |
| Source | |
| Protein | 7.19 g |
| Casein | 3.595 (50%) |
| Soy protein isolate | 3.595 (50%) |
| Carbohydrate | 48.25 g (fiber 2.99 g) |
| Maltodextrin | 31.3 (64.88%) |
| Isomaltulose | 9.97 (20.66%) |
| Fructose | 3.99 (8.27%) |
| Fibersol | 1.99 (4.13%) |
| FOS | 1.00 (2.06%) |
| Fat | 15.95 g |
| Canola oil | 6.98 (43.74%) |
| High-oleic safflower oil | 2.99 (18.77%) |
| MCT oil | 5.98 (37.49%) |
| Micronutrient | |
| Vitamins and minerals | |
| Vitamin A | 67.43 μ g RE |
| Vitamin D | 15.20 IU |
| Vitamin C | 36.27 mg |
| Calcium | 143.6 mg |
| Phosphorus | 143.6 mg |
| Magnesium | 39.06 mg |
| Potassium | 197.4 mg |
| Sodium | 132.8 mg |
| Carnitine | 99.71 mg |
| Others | As recommended by Thailand RDI |

Abbreviations: FOS, fructooligosaccharide; MCT, medium-chain triglyceride; RE, retinol equivalents; IU, international units; RDI, recommended daily intake.

of potassium, and 132.8 mg of sodium. Table 1 summarizes all the components in ORF.

All participants had their medical history reviewed. The assessment consisted of anthropometric measurements, dietary intake, and laboratory tests. Anthropometric measurements such as body weight, height, and body mass index were performed using standard protocols before and after treatment. Casual systolic blood pressure and diastolic blood pressure were measured using a standard mercury sphygmomanometer applied on the same arm after a 10-minute rest in the sitting position.

Dietary intake

All participants kept a 3-day food record and underwent dietary interviews by a registered dietitian, before and after the study period. Nutrient composition of the diets was analyzed with the Inmucal National Food Database Program.

Daily protein intake was determined by the calculated protein equivalence of total nitrogen appearance.¹¹

Laboratory tests

All participants underwent routine laboratory tests including assays for fasting plasma levels of glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, hemoglobin, creatinine, blood urea nitrogen (BUN), calcium, phosphorus, magnesium, albumin, and prealbumin at baseline, and at the end of the trial. All participants performed self-directed 24-hour urine collections and underwent creatinine clearance and urea clearance the next day, during which blood and spot urine samples were also collected. Serum and urine creatinine samples were analyzed using the enzymatic method. GFR, using the Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine, was calculated.

Safety monitoring

Adverse events that were or were not considered to be related to ORF treatment were monitored. The patients were questioned each time in a systematic way regarding their experiences concerning adverse events during the previous week. Patients also underwent blood drawing for safety tests that included complete blood counts and liver function tests.

Statistical analysis

Data were expressed as mean \pm standard deviation, median, or number and percentage. Continuous variables between baseline and at the end of study were compared using paired *t*-tests. All statistical tests were two-sided, and $P < 0.05$ was required to reject the null hypothesis. Statistical analysis was performed using SPSS for Windows, version 16.0 (SPSS, Chicago, IL, USA).

Results

Demographic data and clinical characteristics of 29 nondiabetic CKD subjects are presented in Table 2. The participants were all Thais, 75.9% male with mean age 64.9 ± 13.3 years. Body weight was 65.4 ± 11.3 kg. Mean serum albumin level was 4.4 ± 0.3 g/dL. Mean serum creatinine and estimated GFR were 1.9 ± 0.8 mg/dL and 37.7 ± 12.1 mL/min/1.73 m², respectively.

Dietary intake

Estimated energy and nutrient intake is summarized in Table 3. A significant increase in energy intake from 21.8 ± 6.2

Table 2 Characteristics of the study population

| | N=29 |
|---------------------------------------|------------------|
| Male (n, %) | 22 (75.86%) |
| Age (years) | 64.9 ± 13.3 |
| Height (cm) | 162.6 ± 10.1 |
| Body weight (kg) | 65.4 ± 11.3 |
| Body mass index (kg/cm ²) | 24.7 ± 2.8 |
| Systolic blood pressure (mmHg) | 133.3 ± 14.3 |
| Diastolic blood pressure (mmHg) | 75.9 ± 11.1 |
| Hemoglobin (g/dL) | 13.0 ± 1.7 |
| Prealbumin (mg/dL) | 35.7 ± 6.7 |
| Albumin (g/dL) | 4.4 ± 0.3 |
| AST (U/L) | 23.1 ± 9.1 |
| ALT (U/L) | 19.8 ± 10.2 |
| ALP (U/L) | 72.0 ± 23.9 |
| BUN (mg/dL) | 25.9 ± 15.1 |
| Serum creatinine (mg/dL) | 1.9 ± 0.8 |
| CKD-EPI (mL/min/1.73 m ²) | 37.7 ± 12.1 |

Note: Values are presented as n (%) and mean \pm SD.

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SD, standard deviation.

to 23.3 ± 5.6 kcal/kg/day was noted during the study ($P = 0.044$). At the end of the study, dietary intake of fat and fiber increased significantly by 8.98 ± 11.54 kcal/day ($P < 0.001$) and 2.32 ± 3.88 g/day ($P = 0.003$), respectively. Additionally, calcium intake (349.6 ± 150.3 versus 454.7 ± 154.2 ; $P = 0.016$) and magnesium intake (36.0 ± 17.5 versus 71.6 ± 28.0 ; $P = 0.001$) improved after 1 week of intervention. However, dietary protein intake significantly decreased from 0.9 ± 0.3 to 0.8 ± 0.2 g/kg/day ($P = 0.036$). No significant change was found in other serum electrolytes including sodium, potassium, and phosphorus after intervention.

Nutritional and metabolic parameters

Nutritional and metabolic biomarkers during the period of the study are summarized in Table 4. Overall, nutritional biomarkers including body weight, prealbumin, albumin, and protein equivalence of total nitrogen appearance did not significantly change during the 1-week baseline period. Similarly, metabolic profiles including fasting plasma glucose, lipid profiles, and hemoglobin did not significantly change.

Biochemical and renal function measurement

At the end of the study, BUN decreased significantly by -1.90 ± 4.95 mg/dL ($P = 0.048$), and serum magnesium increased significantly by 0.08 ± 0.16 mg/dL ($P = 0.015$). The treatment did not significantly change the levels of serum

Table 3 Dietary intake with 3-day food record at baseline and at the end of 1-week follow-up

| Per day | Baseline | End | Mean change (95% CI) | P-value |
|----------------------|---------------|---------------|--------------------------|---------|
| Energy (kcal) | 1,394.1±342.1 | 1,495.4±339.9 | 101.38 (9.60, 193.20) | 0.032 |
| Energy (kcal/kg/day) | 21.8±6.2 | 23.3±5.6 | 1.44 (0.01, 2.84) | 0.044 |
| Protein (g) | 58.1±22.2 | 50.9±14.5 | -7.16 (-14, -0.37) | 0.040 |
| Protein (g/kg/day) | 0.9±0.3 | 0.8±0.2 | -0.12 (-0.20, -0.01) | 0.036 |
| Carbohydrate (g) | 200.6±58.1 | 222.1±64.9 | 21.50 (-2.20, 45.21) | 0.074 |
| Fat (g) | 39.3±13.4 | 48.3±13.4 | 8.98 (4.60, 13.37) | 0.001 |
| Fiber (g) | 8.0±4.2 | 10.4±3.8 | 2.32 (0.80, 3.80) | 0.003 |
| Sodium (mg) | 1,934.4±699.1 | 2,111.7±843.6 | 177.21 (-170, 524.47) | 0.305 |
| Potassium (mg) | 1,223.6±407.0 | 1,192.3±364.2 | -31.35 (-188.70, 126.01) | 0.686 |
| Calcium (mg) | 349.6±150.3 | 454.7±154.2 | 104.50 (21.30, 187.73) | 0.016 |
| Phosphorus (mg) | 621.1±164.4 | 636.0±168.9 | 14.90 (-39.90, 69.68) | 0.581 |
| Magnesium (mg) | 36.0±17.5 | 71.6±28.0 | 35.50 (25.60, 45.39) | 0.001 |

Notes: Values are presented as mean ± SD and mean change (95% CI). P-value corresponds to paired t-test.

Abbreviations: CI, confidence interval; SD, standard deviation.

Table 4 Nutritional and laboratory parameters at baseline and at the end of 1-week follow-up

| Variables | Baseline | End | Mean change (95% CI) | P-value |
|--|------------|------------|----------------------|---------|
| Nutrition parameters | | | | |
| Body weight (kg) | 65.6±11.2 | 65.5±11.4 | -0.03 (-0.40, 0.36) | 0.869 |
| Serum albumin (g/dL) | 4.4±0.3 | 4.4±0.3 | 0.04 (-0.10, 0.13) | 0.392 |
| Prealbumin (mg/dL) | 35.7±6.7 | 36.3±8.2 | 0.56 (-1.60, 2.68) | 0.592 |
| nPNA (g/kg/day) | 0.9±0.3 | 0.8±0.3 | -0.07 (-0.20, 0.02) | 0.122 |
| Metabolic parameters | | | | |
| Systolic BP (mmHg) | 130.5±17.1 | 130.2±15.2 | -0.28 (-4.70, 4.09) | 0.898 |
| Diastolic BP (mmHg) | 73.7±12.1 | 74.5±10.7 | 0.86 (-1.70, 3.46) | 0.502 |
| Hemoglobin (g/dL) | 13.0±1.7 | 12.8±1.5 | -0.08 (-0.20, 0.08) | 0.303 |
| FPG (mg/dL) | 95±11.9 | 94.1±12.0 | -0.86 (-3.10, 1.41) | 0.443 |
| Total bilirubin (mg/dL) | 0.5±0.2 | 0.5±0.2 | -0.03 (-0.10, 0.02) | 0.143 |
| AST (U/L) | 21.8±7.9 | 21.2±7.4 | -0.55 (-1.50, 0.37) | 0.229 |
| ALT (U/L) | 19.2±7.3 | 18.6±6.8 | -0.69 (-2.30, 0.96) | 0.398 |
| ALP (U/L) | 71.8±22.3 | 70.7±27.1 | -1.10 (-6.30, 4.11) | 0.668 |
| Serum electrolytes, mineral, and renal parameters | | | | |
| BUN (mg/dL) | 25.9±15.1 | 23.9±14.4 | -1.90 (-3.80, -0.02) | 0.048 |
| Serum creatinine (mg/dL) | 1.9±0.9 | 2.3±1.9 | 0.34 (-0.40, 1.06) | 0.337 |
| Estimated GFR (mL/min/1.73 m ²) | 38.9±13.8 | 36.9±14.3 | -2.03 (-5.90, 1.85) | 0.292 |
| Sodium (mEq/L) | 140.3±2.3 | 140.4±2.3 | 0.09 (-0.60, 0.74) | 0.772 |
| Potassium (mEq/L) | 4.4±0.4 | 4.6±0.4 | 0.05 (-0.10, 0.17) | 0.437 |
| Chloride (mEq/L) | 102.2±3.8 | 102.1±3.6 | -0.15 (-1.10, 0.8) | 0.747 |
| Bicarbonate (mg/dL) | 23.7±3.3 | 24.1±3.2 | 0.37 (-0.30, 1.03) | 0.258 |
| Calcium (mg/dL) | 9.2±0.4 | 9.3±0.4 | 0.06 (-0.10, 0.21) | 0.442 |
| Phosphorus (mg/dL) | 3.4±0.6 | 3.5±0.6 | 0.08 (-0.10, 0.27) | 0.391 |
| Magnesium (mg/dL) | 2.1±0.2 | 2.2±0.3 | 0.08 (0.01, 0.14) | 0.015 |
| 24-hour urine electrolytes and clearance | | | | |
| Sodium (mEq/day) | 29.7±9.5 | 32.7±12.5 | 3.03 (-2.20, 8.26) | 0.245 |
| Protein (g/day) | 0.6±1.3 | 0.5±0.7 | -0.11 (-0.40, 0.17) | 0.419 |
| Urea clearance (mL/min) | 21.9±9.5 | 23.3±13.6 | 0.49 (-5.20, 6.17) | 0.860 |
| Creatinine clearance (mL/min) | 48.3±18.4 | 48.8±25.3 | 1.32 (-1.60, 4.20) | 0.355 |

Notes: Values are presented as mean ± SD and mean change (95% CI). P-value corresponds to paired t-test.

Abbreviations: CI, confidence interval; nPNA, protein equivalence of total nitrogen appearance; BP, blood pressure; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; GFR, glomerular filtration rate; SD, standard deviation.

creatinine, estimated GFR, sodium, potassium, bicarbonate, phosphorus, magnesium, urea clearance, and creatinine clearance.

Safety profile

During the study period, no major complications and gastrointestinal adverse effects were observed. The rate of adverse events with hyperkalemia (potassium >5.5 mEq/L), hypercalcemia (calcium >10.5 mg/dL), hyperphosphatemia (phosphorus >5.5 mg/dL), and elevated liver enzymes among patients given dietary supplement was not detected. At the study's completion, all subjects expressed a desire to continue receiving the ORS supplementation.

Discussion

The present study constitutes the first clinical trial of ORF in CKD patients. The supplement increased energy, fat, and fiber intake and decreased protein intake without changing the serum minerals and electrolytes in a predialysis CKD population. Thus, ORF supplement tends to benefit the predialysis CKD population. However, the finding is a short-term clinical outcome.

Nutritional intervention among predialysis CKD patients is often complicated and costly. Limited evidence exists pertaining to the impact of individualized nutritional intervention by a renal dietitian on clinical outcomes among patients with CKD.¹² Based on the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines in CKD, adults with CKD stage III–IV are recommended a diet with adequate energy to maintain desirable body weight and normal protein near the level of 0.6–0.8 g/kg/day.¹³ In addition, the European Society for Clinical Nutrition and Metabolism guidelines recommend that oral nutritional supplements and tube feeding offer the possibility of increasing nutrient intake in patients with inadequate dialysis and restrict protein intake at 0.55–0.6 g/kg/day in predialysis CKD cases.¹⁴ Our findings revealed that ORF could significantly improve energy and fiber intake and maintain nutritional markers among well-nourished CKD patients with advanced age and normal body mass index. Studies with low-protein diet and oral essential nutrient supplements have reported similar findings. After short- and long-term follow-up, the treatment appears to confirm a maintained nutrition status with a significantly slow CKD progression.^{15,16} Similarly, for patients on maintenance hemodialysis, oral nutritional supplement given during hemodialysis improved nutritional markers among malnourished dialysis patients.¹⁷ Further studies of the efficacy of ORF

regimen with respect to improving clinical outcomes are required regarding malnourished CKD patients.

A recent meta-analysis study evaluating dietary protein intake in a CKD population showed that dietary protein restriction reduced the rate of decline in estimated GFR.¹⁸ However, a subsequently published Cochrane review study evaluating dietary protein restriction found no significant dietary protein restriction on CKD progression.¹⁹ Our findings revealed that ORF significantly reduced protein intake to 0.8 g/kg/day with a lower BUN level and maintained nutritional markers among CKD patients. Additionally, several studies have investigated the beneficial effects of severe hypoproteic diet supplemented with ketoanalogues in advanced CKD patients in a placebo-controlled randomized prospective study. As in our study, their treatments improved nitrogen waste products retention and maintained nutritional status in patients with CKD.^{20,21}

Restrictions of dietary components are often implemented in CKD patients because of an increased risk of uremia, salt retention, hyperkalemia, hyperphosphatemia, negative calcium balance, and metabolic acidosis.²² The Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes guidelines recommend that individuals with CKD receive appropriate dietary advice, tailored to the severity of CKD and the need to intervene on dietary sodium (<90 mEq/day or <2 g/day), potassium (2–4 g/day), and phosphorus (0.8–1.0 g/day) restriction where indicated.^{13,23} Our findings revealed that ORF supplement could achieve the therapeutic targets of dietary intake with an average dietary sodium intake of 2.1 g/day, average 24-hour urine sodium of 34 mEq/day, average dietary potassium intake of 1.1 g/day, and average dietary phosphorus intake of 0.6 g/day. Most importantly, ORF supplement did not disturb serum minerals and electrolyte levels among CKD patients. In contrast, ORF supplement could improve dietary calcium and magnesium intake and serum magnesium levels.

The study had a few limitations. First, the study design was not randomized or placebo-controlled. Second, a selection bias of subjects might exist. Our subjects were mainly the army population and their spouses. This might be one reason why more men than women participated. Third, our study had a short duration of ORF administration and a relatively small number of enrolled patients. Long-term compliance, safety, and efficacy of this diet regimen with respect to improving clinical outcomes require further study.

In conclusion, this prospective study indicated that consuming special renal nutritional formula produces more

energy, fiber, trace elements intake, and less protein intake in predialytic CKD patients. This supplementation might provide a palatable and practical treatment. However, its clinical impact and effectiveness should be further assessed in a larger group of patients over a longer period.

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Disclosure

The authors report no conflicts of interest in this work.

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