ORIGINAL RESEARCH

# Replacing Phosphorus-Containing Food Additives With Foods Without Additives Reduces Phosphatemia in End-Stage Renal Disease Patients: A Randomized Clinical Trial

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**Objective:** The purpose of the study was to verify the effects of replacing phosphorus-containing food additives with foods without additives on phosphatemia in end-stage renal disease (ESRD) patients.

**Design:** Randomized clinical trial.

**Setting:** Adult patients on hemodialysis for ≥6 months at a single center.

**Subjects:** A total of 134 patients with phosphorus levels of >5.5 mg/dL were included and were randomized into an intervention group (n = 67) and a control group (n = 67).

**Intervention:** The IG received individual orientation to replace processed foods that have phosphorus additives with foods of similar nutritional value without these additives. The CG received only the nutritional orientation given before the study. Clinical laboratory data, nutritional status, energy and protein intake, and normalized protein nitrogen appearance (nPNA) were evaluated at the beginning of the study and after 90 days.

**Results:** There was no initial difference between the groups in terms of serum phosphorus levels, nutritional status, and energy intake. After 3 months, there was a decline in phosphorus levels in the IG (from 7.2 ± 1.4 to 5.0 ± 1.3 mg/dL, $P < .001$), but there was no significant difference in the CG (from 7.1 ± 1.2 to 6.7 ± 1.2 mg/dL, $P = .65$). In the IG, 69.7% of the patients reached the serum phosphorus target of ≤5.5 mg/dL; however, only 18.5% of the CG subjects reached this level ($P < .001$).

**Conclusion:** At the end, there was no difference between the two groups in terms of nutritional status, energy intake, protein intake, and nPNA. The replacing phosphorus-containing food additives with foods without additives reduced serum phosphorus without interfering in the nutritional status of ESRD patients.



## Introduction

HYPERPHOSPHATEMIA IS FREQUENT in patients who have chronic renal disease (CRD) and are on hemodialysis, and it is associated with increased risk for cardiovascular diseases, atherosclerotic events, secondary hyperparathyroidism, and bone disease.[1,2] It is also an independent risk factor for increased mortality in patients with end-stage renal disease (ESRD).[3,4] Epidemiologic studies suggest that higher serum phosphate levels, even levels that are well within the normal range, are associated with an increased risk for cardiovascular disease.[5,6] The treatment and prevention of hyperphosphatemia is one of the main objectives in the treatment of patients with ESRD. Phosphorus-binding agents and phosphorus-intake restriction are used to achieve this objective.[7,8] However, phosphorus-intake restriction is associated with protein-intake restriction and a risk of malnutrition.[4–8]

A phosphorus-restricted diet is based on the reduction of foods containing large quantities of the mineral, such as meats, dairy products, whole grain cereals, legumes, and nuts. Furthermore, studies show that the phosphorus in foods is available in both organic and inorganic forms.[9] Organic phosphorus, which is naturally present in foods, has a 60% absorption rate,[10] whereas inorganic phosphorus, which is added to industrialized foods, is absorbed at an estimated rate of 90%.[11] The additives (i.e., phosphorus salt or phosphoric acid) present in industrialized products preserve these foods colors, maintain their moisture, improve their flavor, homogenize their ingredients, and stabilize their proteins.[12,13] The consumption of foods with phosphorus additives has increased in recent decades due to their easy accessibility, which makes nutritional counseling on the reduction of phosphorus intake even more difficult for dialysis patients.[14] In the United States, the average phosphorus intake of men and women in 2009-2010, as measured by the National Health and Nutrition Examination Survey, exceeded the recommended daily allowance

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by up to 2 times.[15] In many countries, the phosphorus intake of the general population and of patients with kidney disease is not well known.

Bell et al. conducted one of the main studies on the effects of phosphorus additives on phosphatemia in healthy subjects,[16] and it showed a significant increase in serum and urinary phosphorus levels. Sullivan et al. showed that the dietary restriction of phosphorus additives in patients who were on hemodialysis had a beneficial effect on phosphatemia, but the patients' protein intake, energy intake, and nutritional status were not considered in the study.[17]

Considering the lack of studies on the dietary restriction of phosphorus additives and the repercussions for nutritional status, we verified the hypothesis that replacing foods that have phosphorus additives with foods that do not have phosphorus additives reduces phosphatemia and maintains the nutritional status of ESRD patients.

## Participants and Methods

### Patients

This randomized trial was conducted with adult patients who had ESRD and were on hemodialysis at a single center. The Ethics Committee approved the study in November 2011 and the study was conducted in accordance with the guidelines in the Declaration of Helsinki. Written informed consent was obtained from all patients prior to their inclusion in the study. The study was registered at clinicaltrials.gov (NCT01965379). There was not an ongoing related trial.

The inclusion criteria were as follows: hemodialysis treatment for at least 6 months; both sexes; aged ≥18 years; persistent serum phosphorus levels of ≥5.5 mg/dL (at least 3 measurements) during the previous 3 months; absence of infection and neoplasia; preserved cognitive capacity; and reading and writing skills. The exclusion criteria were as follows: the use of enteral or parenteral therapy; the presence of physical limitations; cognitive limitations, or malabsorption diseases. Before the study began, the facility's registered dietitian provided all the participants with a nutritional orientation on the usual renal diet and the importance of restricting the intake of foods rich in phosphorus. The participants also received a nutritional booklet from the dietitian and the nutritional counseling was reinforced each month after the patients received their biochemical test results.

A total of 267 patients were evaluated for eligibility, and 140 patients were randomized into either the intervention group or the control group. According to the sample size calculation, 70 patients were necessary for the intervention group and for the control group (80% power). In the intervention group, three patients were lost (two patients received a transplant and one patient refused to participate); thus, a total of 67 patients were included for primary analysis. Three patients were also lost in the control group (two patients were moved to another facility, and one patient refused to participate). During the follow-up period, one patient was lost from the intervention group, and two patients were lost from the control group. Therefore, 66 intervention group patients and 65 control group patients completed the study. (A flow cart of the study is presented in Fig. 1).

The nutritional status, biochemical parameters, dietary intake of energy, protein, and phosphorus, and normalized protein nitrogen appearance (nPNA) were assessed in both groups at baseline and after 90 days (at the end of the study) by the study dietitian.

### Baseline Assessment

The demographic, clinical, and laboratory characteristics of the intervention and control participants were obtained from medical records. The biochemical tests measuring serum creatinine, urea, hemoglobin, serum albumin, and phosphorus levels were performed using an automatic method; serum ionized calcium and intact parathyroid hormone levels were assessed using immunoassays and chemoluminometric assays (ADVIA Centaur, Siemens Healthcare Diagnostics, Erlanger, Germany), respectively. Ionized calcium was used in this study because it is recommended for CRD patients.[18,19] The mean values of the biochemical parameters (measured during the previous 3 months) were considered.

The patients underwent hemodialysis 3 times per week for 4 hours; a standard dialysis bath, a cellulose triacetate dialyzer (2.1 $m^2$), and a Nipro dialysis machine (Surdial model, Osaka, Japan) were used. The Kt/V was calculated using Dialsist 2.5 software.

Initially, the researcher (who was not blinded) performed individual nutritional interviews; the interview included a 24-hour dietary recall, a food frequency questionnaire,[20] and questions to assess the patient's knowledge about the renal diet.[21,22]

Anthropometric measurements were obtained postdialysis and included body mass index (BMI, $kg/m^2$), triceps skinfold thickness (TSF, mm), mid-arm muscle circumference (MAMC, cm), and mid-arm muscle area (AMA, $cm^2$). AMA was calculated from TSF and mid-arm circumference (MAC, cm) and corrected sex using the following formulas: AMA (corrected for males) = $[(\text{MAC (cm)} - \text{TSF (cm)}^2)/4 \times \pi] - 10$; and AMA (corrected for females) = $[(\text{MAC (cm)} - \text{TSF (cm)}^2)/4 \times \pi] - 6.5$.[21,23] The TSF was measured at the mid-point of the upper arm opposite the arteriovenous fistula with a Lange Skinfold Caliper (Beta Technology Incorporated, Cambridge, Maryland, USA). MAMC has been validated in hemodialysis patients and has been shown to be associated with a survival advantage.[24]

### Dietary Intake

The dietary recalls and food diaries were analyzed to calculate the energy and protein intake in both groups and to assist in the dietary counseling of the patients in