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The impact of a nutritional intervention based on egg white for phosphorus control in hemodialyis patients

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Abstract *Background and aims:* Here we describe a dietary intervention for hyperphosphatemia in dialysis patients based on the partial replacement of meat and fish, which are one of the main sources of alimentary phosphorous, with egg white, a virtually phosphorous-free protein source. This intervention aims to reduce phosphorous intake without causing protein wasting.
Patients and methods: As many as 23 hyperphosphatemic patients (15 male and 8 female, mean age 53.0 ± 10.0 years) on chronic standard 4 h, three times weekly, bicarbonate hemodialysis were enrolled in this open-label, randomized controlled trial. Patients in the intervention group were instructed to replace fish or meat with egg white in three meals a week for three months whereas diet was unchanged in the control group.
Results: Serum phosphate concentrations were significantly lower in the intervention group than in controls after three (4.9 ± 1.0 vs 6.6 ± 0.8; $p < 0.001$) but not after one month of treatment. Phosphate concentrations decreased more from baseline in the intervention than in the control group both after one (−1,2 ± 1,1 vs 0,5 ± 1,1; $p = 0.004$) and after three (−1,7 ± 1,1 vs −0,6 ± 1,1; $p < 0.001$) months of follow-up. No change either in body weight or in body composition assessed with bioelectrical impedance analysis or in serum albumin concentration was observed in either group.
Conclusion: The partial replacement of meat and fish with egg white induces a significant decrease in serum phosphate without causing protein malnutrition and could represent a useful instrument to control serum phosphate levels in hemodialysis patients.
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Introduction

Hyperphosphatemia develops in the majority of patients with end-stage renal disease (ESRD). It has a role in worsening the cardiovascular mortality of dialysis patients and is responsible for severe complications such as mineral bone disease [1,2]. Therefore, a close control of serum phosphate remains a cornerstone in the clinical

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management of dialysis patients to improve their long-term prognosis. According to the 2003 KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease [3], phosphate levels in plasma should be kept in the 3.5–5.5 mg/dl range and the Ca*P product should be less than 55 mg^2/ml^2. Hemodialysis (HD) alone is not effective in matching these targets that can be reached only if it is combined with the use of phosphate binders, a class of drugs that decrease phosphate absorption in the gut, and with a specific nutritional approach to lower phosphorous intake [4,5].

There are multiple sources of phosphorus in the diet that could be the target of such a dietary intervention but, because of important differences in bioavailability, they are not all equally relevant in influencing phosphatemia [6]. The bioavailability of organic phosphorus depends on its origin and is low in plants (e.g., phytates) whereas it ranges around 60% in animal proteins (e.g., casein). Therefore, animal proteins are a way more important target for a phosphate-lowering nutritional intervention than plants as also suggested by the evidence that in HD patients there is a positive correlation between animal protein intake and phosphatemia [6].

While reducing animal protein intake seems a feasible approach in the conservative treatment of non-dialysis patients with chronic kidney disease (CKD), it is much more problematic in dialysis patients because they have high protein requirements. Indeed, the recommended dietary protein intake for clinically stable HD patients is 1.2 g/kg body weight/day, 50% of which should come from sources high in biological value [7]. Reducing protein intake below these recommended values may be dangerous in HD patients because it increases the risk of malnutrition hence worsening their prognosis [8]. Therefore, alternative nutritional approaches that could lower phosphorous intake without inducing protein malnutrition could be helpful in HD patients. In this perspective, here we report the encouraging results that we obtained by substituting egg white for other animal proteins in the diet of a group of HD patients. Although egg white has high protein content ranging around 3.7 g for one egg white, its phosphorus content is close to zero. This establishes an important difference from other animal protein sources also including egg yolk, and represents the rationale of testing egg white in HD patients as a tool to lower phosphorus intake without impoverishing the protein content of the diet.

Methods

Study design

The present study was a two-arm, open-label, randomized controlled trial. Study protocol was approved by the Federico II ethics committee (#76/17) and informed consent was obtained from all individual participants included in the study. Study procedures were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was performed in HD patients with hyperphosphatemia. Inclusion criteria were: three times weekly 4 h standard bicarbonate HD treatment with an at least 6-month vintage and with stable dialysis dose and modality, hyperphosphatemia (serum phosphate ≥5.0 mg/dl), stable dietary intake, body weight and biochemical markers at least by 3 months. Exclusion criteria were: diabetes, liver disease, malignancy, previous parathyroidectomy or psychiatric diseases. Non-collaborative patients were excluded as well. Using a computer-generated list the patients enrolled in the study were randomized in two groups, *intervention* and *control*. During the study patients of the control group continued to follow a Mediterranean style diet. In the *intervention* arm patients were instructed to replace three times weekly, only in one meal of the day, fish or meat with an adequate amount of egg white to keep protein intake unmodified. We gave the patients specific practical suggestions on how this diet modification could be obtained. For instance, we advised replacing one serving of meat (i.e. 120 g) with 5.5 egg whites or one serving of fish (i.e. 150 g) with 6 egg whites suggesting alternative cooking methods such as smoothies, veggie casseroles, egg salads, scrambles or omelets. We did not specify the meal of the day in which egg white had to substitute for fish or meat and the patient were free to make this replacement either at lunch or at dinner according to their preferences. The planned duration of the nutritional intervention was three months. Adherence to the diet was assessed monthly in all patients through interviews conducted by dietitians using a food-frequency questionnaire that includes 131 foods and beverages [9]. More specifically, in this questionnaire, patients are asked how many servings (as defined in the questionnaire) of each food they consumed during the period of interest. The data obtained are then converted into daily intakes considering the time span evaluated during the interview. Food intakes are used to estimate nutrient intakes by the means of specific tables that report the nutrient composition of each food. Specifically we used the tables of the Italian National Institute of Nutrition, the Souci's Food Composition Tables and the Nutrition Tables of the European Institute of Oncology [10–12]. During the study the patients continued their drug therapy unmodified, including phosphate binders, recombinant erythropoietin and vitamin D3 analogues.

The primary endpoint was changes in serum phosphate whereas the lack of major changes in body composition, serum albumin and hemoglobin levels were secondary endpoints.

Sample size calculation was performed with the G*Power 3.1.9.2 software (http://www.gpower.hhu.de/). Specifically, assuming that the expected average of serum phosphate before starting the trial was 6.0 ± 0.8 mg/dL we estimated that at least 10 patients per group were required to detect a 15% change in serum phosphate down to 5.1 ± 0.4 mg/dL.

At the time of the first visit, a through clinical examination with the measurement of anthropometric parameters and bioelectrical impedance analysis (BIA) was performed. Patients underwent follow-up visits with a similar protocol one and three months later. A blood sample for the determination of serum calcium and phosphate and of other chemicals was collected approximately at the same time of the day, early in the morning before the first weekly hemodialysis session. Conversely, clinical and instrumental examinations including body weight determination and BIA were performed 30 min after the end of a hemodialysis session.

BIA was performed with the standard tetrapolar technique measuring resistance (Rs) and reactance (Xc) at 50 kHz with a BIA 101 RJL bioelectrical impedance analyzer (Akern Bioresearch, Firenze, Italy) [13].

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for Social Science (SPSS) Advanced Statistics software (release 20.0) (Armonk, New York, USA) for Windows. Data were examined for normality using the Shapiro–Wilk test and expressed as mean ± standard deviation if normally distributed and as median and interquartile range if not.

Intra- and intergroup statistical comparisons of phosphate serum levels and of the other chemicals at the different time points of the study were performed with two-ways repeated measure ANOVA followed by the Bonferroni post hoc test. The threshold for statistical significance was set at $P < 0.05$ with Bonferroni correction.

Results

Study population consisted of 23 hyperphosphatemic patients (15 male and 8 female, mean age 53.0 ± 10.0 years) on chronic standard 4 h, three times weekly bicarbonate hemodialysis that were randomized in two groups, control and intervention. As shown in Table 1, there was no significant difference between these two groups in any of the demographic, anthropometric and laboratory characteristics or in their drug therapy. No patient was on anabolic steroids or protein supplements. All patients completed the study and there was no dropout; no patient from either group developed infections or was admitted to the hospital.

No difference in the energy and protein intake estimated from patient dietary interviews was observed between intervention and control groups either at baseline or after three months of treatment, with the only exception of dietary phosphorous and phosphorous/protein ratio that significantly decreased in intervention group (from 1066 ± 122 to 971 ± 103 and from baseline 13.8 ± 1.7 to 12.4 ± 0.8, respectively; $p < 0.05$) and remained unmodified in the control group (Table 2).

Although one month after the beginning of the study serum phosphate concentrations were not significantly different in the control and in the intervention group, we observed a significant difference in the change of serum phosphate concentration from baseline (−1,2 ± 1,1 vs 0,5 ± 1,1, respectively; $p = 0.004$). At the second follow-up, both serum phosphate concentration (4.9 ± 1.0 vs 6.6 ± 0.8; $p < 0.001$) and their change from baseline were significantly different in the intervention and control group (−1,7 ± 1,1 vs –0,6 ± 1,1, respectively; $p < 0.001$) (Table 3 and Fig. 1).

To assess whether our nutritional intervention caused malnutrition or negatively affected body composition we compared the data of BIA obtained at the time of the first visit and at the end of the study and we did not find any significant difference in Rs, Xc, phase angle or fat free mass, neither in the intervention or in the control group. Moreover, both serum albumin and Hb concentrations remained stable across the study further suggesting that a good nutritional status was preserved in our patients (Tables 2 and 3).

Table 1 Baseline characteristics of the study participants.

	Intervention	Control
Number	13	10
M/F	8/5	7/3
Age (years)	50.5 ± 11.5	53.7 ± 10.6
Body weight (kg)	86.1 ± 19.5	90.1 ± 21.5
Body mass index (kg/m^2)	31.0 ± 5.6	34.0 ± 5.8
Serum phosphate (mg/dl)	6.6 ± 1.0	5.9 ± 0.7
Sevelamer use (*n* [%])	4 (30)	4 (40)
Lanthanum use (*n* [%])	4 (30)	3 (30)
Use of vitamin D derivatives (*n* [%])	5 (38)	3 (30)

Discussion

The main finding of the present study was that in HD patients serum phosphate levels decreased to normal levels when fish and meat were replaced with egg white in three meals a week.

The serum phosphate lowering effect of this dietary modification can be explained by the decrease in phosphorous intake that it caused. Indeed, with this intervention meat and fish proteins, which are one of the main phosphorous sources in the diet [14,15], were replaced with egg white that has the lowest phosphorous to protein ratio among all natural foods [6]. It is remarkable that serum phosphate normalization was obtained by substituting egg white for other animal proteins just three times a week. Indeed, assuming that the average content of the phosphorus content in meat can vary from 170 to 290 mg/100 g, while in fish it varies from 190 to 290 mg/100 g [10], the expected phosphorous content of a typical meat or fish serving will be about 250 mg and, consequently, with our dietary intervention the total phosphorous weekly intake should decrease by 0.75 g/week from its mean value of 6–14 g/week. Therefore, the total weekly phosphorus intake in patients on our egg white-based dietary intervention should be still higher than the maximum amount of phosphorous that can be removed by HD (on average 2.4–3.6 g/week) [16] and hyperphosphatemia should not be corrected. However, only about 60% of the ingested phosphorus is absorbed from the gut and by removing meat and fish we actually removed the phosphorous sources with the highest oral bioavailability. It is also worth to mention that meat is among the most important alimentary sources of

Table 2 Mean dietary intakes and bioelectrical impedance data in the Intervention and in the control groups at baseline and at the end of the study.

	Intervention (n = 13)		Control (n = 10)	
	Baseline	3 months	Baseline	3 months
Energy (kcal/kg[a]·day)	28.1 ± 2.3	28.0 ± 2.4	28.0 ± 2.3	27.6 ± 2.4
Protein (g/kg[a]·day)	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1
Phosphorous (mg/day)	1066.2 ± 122.1	971.4 ± 103.4	1065.2 ± 90.6	1086.1 ± 110.0
Phosphorus/protein ratio (mg/g)	13.8 ± 1.7	12.4 ± 0.8*	14.7 ± 1.2	15.1 ± 1.1
Potassium (mg/day)	2099.6 ± 196.3	2093.8 ± 206.7	1922.8 ± 434.4	1831.5 ± 348.2
Resistance (Ohm)	490.6 ± 62.6	484.0 ± 62.7	512.4 ± 74.3	507.0 ± 62.4
Reactance (Ohm)	55.2 ± 13.2	52.4 ± 12.8	57.2 ± 9.5	56.7 ± 8.9
Phase angle (degrees)	6.3 ± 1.7	6.2 ± 1.7	6.5 ± 0.8	6.5 ± 1.1
Fat free mass (Kg)	56.9 ± 10.7	57.0 ± 10.9	53.6 ± 11.5	53.6 ± 10.3

*$p < 0.001$ vs the respective time point of the control group.
[a] Ideal weight.

phosphorous additives and, therefore, by reducing its amount in the diet a decrease is expected not only in organic but also in inorganic phosphorous intake [17].

Unlike the conventional phosphate-lowering low-protein diets the egg white-based diet that we propose here is expected not to cause protein malnutrition because egg white has a high protein content and a high nutritional value as also demonstrated by the fact that it has been used to increase serum albumin concentration in peritoneal dialysis patients [18]. Our data confirmed these expectations because we did not observe any change in body composition as assessed with BIA in the intervention group. Indeed, no significant change in body weight or in fat free mass was documented and both phase angle and vector length, which are respectively representative of body cell mass and of the hydration status, remained unchanged after 3 months of treatment. Furthermore, in the intervention group serum albumin, which significantly decreases in protein malnutrition and whose decrease predicts higher mortality in HD patients [19], remained unchanged. The ability of an egg white-based diet to normalize serum phosphate without inducing protein malnutrition could have relevant practical implications in the treatment of hyperphosphatemia in HD patients considering that despite treatment in the majority of these patients (60% of HD patients in the United States) serum phosphorus levels are above the KDOQI upper target level of 5.5 mg/dl [20]. This can be due to the reluctance of nephrologists to recommend an aggressive reduction in animal protein intake because they are afraid of inducing or worsening protein energy wasting (PEW) in their patients [21–23]. PEW is a multifactorial condition believed to be the consequence of multiple factors such as the release of proinflammatory cytokines, the activation of hypercatabolic states or the decline in appetite [24]. This condition characterized by the insidious loss of body fat and somatic protein and associated with hypoalbuminemia, chronic inflammation, sarcopenia and weight loss, may cause a substantial worsening of prognosis in HD patients [25–27]. PEW is highly prevalent in HD patients and associated with adverse clinical outcomes, hospitalization, higher morbidity and mortality rates [25–28]. Therefore, when HD patients are required to reduce their protein intake to lower serum phosphate, the benefits obtained with phosphorous intake reduction could be reverted by accompanying protein malnutrition [28–30]. In this perspective, the nutritional strategy that we tested in the present work could represent an effective way to reduce phosphorous but not protein intake in HD patients. By this approach, the nutritional profile that seems to be associated with the lowest mortality in HD-CKD patients, i.e. a high protein intake with and a concurrent low phosphorus intake and with normal serum phosphate seems, could be reproduced in dialysis patients [2,30].

Table 3 Body weight and biochemical markers at baseline and after 1 and 3 months in the Intervention and in the control groups.

	Intervention (n = 13)			Control (n = 10)		
	Baseline	1 month	3 months	Baseline	1 month	3 months
BW (kg)	86.1 ± 19.2	84.3 ± 19.5	83.8 ± 19.1	90.2 ± 21.5	89.9 ± 20.8	89.9 ± 20.3
Serum phosphate (mg/dl)	6.6 ± 1.0	5.4 ± 1.4	4.9 ± 1.0°	5.9 ± 0.7	6.4 ± 1.3	6.6 ± 0.8
Serum phosphate (mg/dl) (change from baseline)	–	−1,2 ± 1,1*	−1,7 ± 1,1°	–	0,5 ± 1,1	0,6 ± 1,1
Creatinine (mg/dl)	10.9 ± 2.2	10.7 ± 3.0	10.9 ± 2.7	10.6 ± 1.9	10.1 ± 2.2	10.1 ± 2.0
BUN (mg/dl)	84.8 ± 17.7	79.3 ± 20.9	74.5 ± 19.9	70.3 ± 12.9	85.1 ± 22.2	79.3 ± 21.4
Albumin (g/dl)	4.0 ± 0.2	4.1 ± 0.4	3.9 ± 0.3	3.9 ± 0.5	3.7 ± 0.3	3.7 ± 0.4
Total Protein (g/dl)	6.9 ± 0.4	6.7 ± 0.6	6.6 ± 0.5	6.8 ± 0.6	6.9 ± 0.7	6.5 ± 0.4
Hemoglobin (g/dl)	11.6 ± 0.9	11.4 ± 1.1	11.6 ± 1.3	11.0 ± 1.3	10.9 ± 0.8	11.6 ± 1.1

*$p < 0.004$ vs the respective time point of the control group; ° $p < 0.001$ vs the respective time point of the control group.

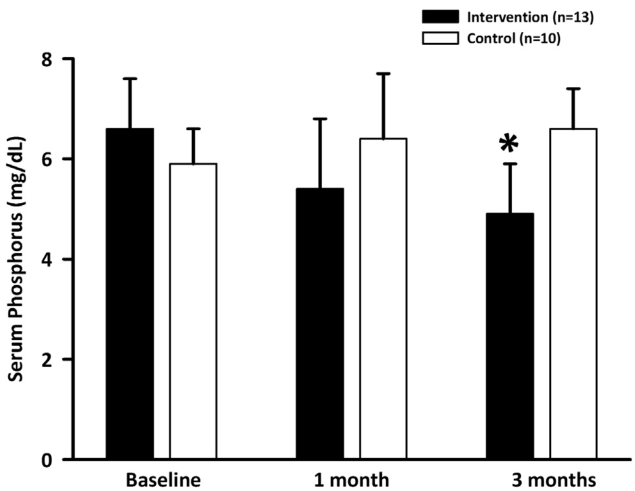

Figure 1 Serum phosphate concentration at baseline and after 1 and 3 months, in the *intervention* (black) and *control* (white) groups. Bars represent mean values and error bars SD of mean. *$p < 0.05$ vs control group.

An additional argument to suggest the use of egg white in HD patients is that this nutritional intervention was well accepted by our patients who were highly adherent to the dietary intervention as assessed with alimentary questionnaires and there was no drop-out from the study. This was a remarkable result because adherence is a problem commonly encountered when implementing nutritional interventions in HD patients. This can be explained by patient frustration due to the limited amount and number of aliments that they are allowed to eat in order to lower the intake of fluids, sodium and potassium. Therefore, different from Taylor et al. [31] who tested egg white in HD patients in a small non-randomized study, we did not give the egg white as a pasteurised liquid, but we instructed to prepare it in several tasty ways such as smoothies, veggie casseroles and egg salads. We believe, indeed, that the in the way food is prepared and served variety is a key factor for long term compliance in dietary treatments.

It is also important to emphasize that the cost for the patients of the egg white-based diet that we described in this paper is negligible. This is an important difference from other dietary interventions for hyperphosphatemia that have been proposed in the past such as the use of a low-phosphorus and low-potassium protein concentrate that we suggested a few years ago [32].

Our study has some important limitations. First, this was a pilot study with a small number of enrolled patients and a short duration of follow-up. Second, because baseline serum phosphate levels were much closer to the lower limit of inclusion in the control than in the intervention group, we cannot exclude that our results could have been biased by the phenomenon of regression to the mean. Third, because changes in protein status were not our primary endpoint, our study could have been underpowered to detect changes in this parameter. Finally, a relevant limitation of our study is actually intrinsic to all the studies that use FFQs to estimate phosphorous intake. Indeed, the currently available food composition tables in books or software programs do not accurately reflect the additional phosphorus from additives content in food that mainly come from milk and dairy products and to a lesser extent from meat and poultry, showing large variations when similar products are compared [33,34]. The relevance of the problem of the current lack of detailed information on phosphate additives has also been acknowledged by the European Food Safety Authority (EFSA) that in 2017 published a call on this specific issue [35]. As far as the present study is concerned, we cannot exclude that our findings were biased by changes in the intake of phosphorous from additives in the two study groups during the investigation even though this seems quite unlikely because patient diet remained unmodified with the only exception of egg replacement in the intervention group. In clinical practice the inability to track and correct all unintended sources of phosphate in the diet may significantly decrease the effectiveness of therapeutic interventions aiming to prevent hyperphosphatemia in CKD patients [33,34]. Therefore, it is expected that, as for any other phosphate-lowering treatment, also the effectiveness of our egg replacement strategy could be maximized only with a specific nutritional education of both patients and health-care professionals aiming to reduce phosphorous intake from unwanted and not accurately measurable sources [36].

In conclusion, we showed that a nutritional intervention based on the replacement of meat and fish protein with egg white induces a significant decrease in serum phosphate without causing protein malnutrition or changes in body composition. This approach could represent a useful instrument to improve the control of serum phosphate in HD patients.

Conflicts of interest

The authors declare that they have no conflict of interest to disclose.

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