



ORIGINAL RESEARCH PAPER

Nephrology

HYPERPHOSPHATEMIA IN HAEMODIALYZED PATIENTS

KEY WORDS: Phosphate, Haemodialyzed patients, Diabetes, Haemodialysis

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ABSTRACT

Dietary regulation of serum phosphate levels is one of the most important therapies for the haemodialyzed patients. This is particularly difficult to apply since these patients must take huge amount of animal proteins that contain a large quantity of phosphate. However, a diet with a small amount of phosphate is required. This guideline is difficult to be implemented because patients get at least 50% of their phosphate from sources that are not obvious and from foods that are easily processed and preserved. In this retrospective study, serum levels of phosphate, calcium and parathyroid hormone were assessed in 123 haemodialyzed patients to determine their levels and differences, depending on age. Patients were grouped into two according to their age. Group A included those who were ≤ 70 years old (n = 55, 29M/26F), and Group B were those > 71 years old (n = 68, 39M/29F). Higher phosphate levels were found in Group A with a statistically significant level of p < 0.0001, while overall serum phosphate levels of 47% of patients were below 4.6 mg/dl. Elderly patients with more diabetics (Group B) had lower serum phosphate levels than the younger ones (Group A). Thus, a large percentage of our patients have satisfactory serum phosphate levels, and the younger ones have less satisfactory phosphate levels, compared with the elderly.

INTRODUCTION

The body's phosphate (Pi) plays a critical role in the biological process, and the majority of it is found in bones and teeth (85%). However, intracellular Pi account for 14% of the body Pi; whereas only 1% is found in the blood. Pi balance in haemodialyzed patients depends on diet (1,2), dialysis type (haemodialysis or haemodiafiltration) and phosphate binders taken.

Patients' education is critical for understanding foods that contain Pi. They must understand that plant foods contain low Pi per serving, which is absorbed in a lower rate. Contrarily, animal foods have various Pi bioavailability (2). Thus, foods with the lowest Pi/albumin ratio are the non-dairy products; whereas animal proteins with low Pi content are egg whites (3). It is found that the Pi content (mg/100 g serving) is highest in various natural food groups such as nuts, hard cheeses, egg yolks, meat, poultry and fishes (4,5). However, the importance of additives in preserved and processed foods should not be forgotten.

Studies have shown that a moderate to negative correlation exists between dietary Pi intake and serum levels (6,7). Additionally, the amount of Pi excreted in the urine is used to measure the Pi intake through food. Numerous randomized control studies have demonstrate the importance of reducing urinary Pi with phosphate binders, with little change in serum Pi levels (7). According to the KDIGO guidelines, there are insufficient data to support that restriction of food intake with high Pi levels is a key intervention in the management of bone disease, especially for patients undergoing haemodialysis and those who fail to have desired serum Pi levels (8). This

study aims to determine whether the regulation of the serum Pi levels in haemodialyzed patients is satisfactory and identify those with better serum Pi levels, based on age.

Patients and Methods

The levels of Pi, total calcium (Ca²⁺) and parathormone (PTH) in 123 haemodialyzed patients were retrospectively studied. Moreover, 12-month values of the above parameters were examined, and the mean value was used. Differences in Pi, Ca²⁺, and PTH were determined between subjects. Patients were grouped into two based on their age. Group A was those ≤ 70 years old (n = 55, 29M/26F), and Group B was those > 71 years old (n = 68, 39M/29F).

Included criteria were patients on dialysis for more than 12 months and patients with records of the above parameters for more than 12 months. Serum Pi values < 4.65 mg/dl were considered normal.

All patients, before starting dialysis (at stages 3-5) and those on dialysis, were contacted frequently. Full information about the sources of Pi and the problems created by high levels of Pi in the body were collected. Additionally, patients received a manual with a complete analysis of the recommended diet to follow.

The 82 patients were on haemodialysis for 4-5:30 hours/session and the 41 patients were on on-line hemodiafiltration. The filters used were polymerized polyester (n = 33) and polyethersulfone (n = 90), with a surface area of 1.9-2.2 m². Unfractionated heparin was used in 3 patients (2000 IU loading dose and 700-1000 IU/h

thereafter), heparin low molecular weight (bemeparin) in 118 patients (dose 2500-3500 U/session) and fondaparinux in 2 patients (2.5 mg/session).

Statistical Analysis

Group A and Group B were compared in terms of serum Pi, Ca²⁺ and PTH values using a non-parametric method (Mann-Whitney U test). These groups were also compared in terms of their qualitative characteristics using a Chi-Square test. The relationship between age and serum Pi levels was studied using regression analysis. A p < 0.05 was considered statistically significant.

RESULTS

A statistically significant difference was shown in Group A and B in terms of age (57±9 years vs. 80±5 years, p < 0.0001). While these groups did not differ in terms of gender (29M/26F vs. 39M/29F, p = NS), Group B had a statistically significant higher percentage of diabetes (x²-test [Fisher's Exact Test], 14/55 vs. 35/68, p < 0.005).

Table 1: Statistical data analysis of groups A and B. As shown, Pi was significantly higher (5.2±1.4 vs 4.3±0.9, p < 0.0001) in the younger patients (group A).

	Group	n	Mean	Std. Deviation	Std. Error Mean	p =
Age	A	55	57,2	9,9	1,3	0.0001
	B	68	80,1	5,7	0,7	
Ca ²⁺	A	55	9,3	0,5	0,06	NS
	B	68	9,1	0,5	0,06	
Pi	A	55	5,2	1,4	0,2	0.0001
	B	68	4,3	0,9	0,1	
PTH	A	55	526	665	89	0.0001
	B	67	222	177	21	

A regression analysis was used to determine the relationship between age and serum Pi levels, in which the factors associated with the serum Pi levels in the specific patients were examined. Pi levels were found to be age-dependent. However, Ca²⁺ serum levels were not age dependent, but PTH was (p=0.0001). Moreover, elderly patients with more diabetics had lower Pi levels than the younger ones (Group A).

DISCUSSION

Plant foods do not yield much Pi because humans do not have the enzyme phytase in their intestine, which is phytate hydrolysis, where Pi is found (9). Thus, only approximately 20-40% of plant versus 40-60% of animal sources of ingested Pi is absorbed in the duodenum and ileum, which increases with the presence of vitamin D (2). A Western man with a body weight of 70 kg takes in an average of 20 mg Pi/kgBW daily (~400 mg/24 hours), and this man mainly absorbs 13 mg/kgBW (~1000 mg/24 hours) in the ileum, in contrast with haemodialyzed patients who take in 1.1 mg/kgBW daily (800-1000 mg/24 hours). A person on dialysis with end-stage renal disease (ESRD) will lose in a 4-hour dialysis session the 30% of the absorbed Pi (~1000 mg), i.e., 3000 mg/week; whereas the other 30% is eliminated through the intestine using the phosphate binders (10).

Animal proteins (i.e., meat, fish, eggs) are the major sources of ingested Pi (11). Moreover, additives are present in many foods because they provide to the foods a longer shelf life, freshness, moisture and colour. Additives also enhance food taste and emulsify their ingredients (12). Also reported, soda and soft drinks contain Pi, and estimated that one in two Americans drinks 1500 ml of soft drinks daily. The most common Pi-containing additives are dicalcium phosphate, hexametaphosphate, monocalcium phosphate, phosphoric acid, pyrophosphate, sodium pyrophosphate, sodium phosphate, sodium tripolyphosphate and calcium phosphate, which are listed on the packaging as E (E338, E343, E442,

E450, E544, E545). However, the high Pi content of products containing additives makes patients face difficulties in adhering to the guidelines for reducing Pi intake. For example, two servings of chicken products containing additives provide an average of 880 mg Pi (13). More importantly, all the Pi of food additives is absorbed (100% bioavailability) (2). In one study, 46% of dialysis patients were unaware that phosphate-containing preservatives were added to processed foods, and only 25% of patients were aware of the presence of Pi in soda (14). For these reasons, the patients' education should contribute to the reduction of the consumption of processed inorganic Pi foods. With this education, patients would be informed about the sources of Pi and additives. Nevertheless, people with high serum Pi values are unable to determine the Pi source responsible for the enhancement of serum levels.

The elevation of serum Pi in dialyzed patients may indicate poor adherence (compliance) to the diet. Kutner et al. noted that Pi levels above 7.5 mg/dl were present only in those who failed to comply with dietary guidelines (15). It is also found that a large percentage of haemodialyzed patients do not follow Pi diet guidelines, mainly because of a large quantity of food intake (16), which is the case of fewer than 5 patients in our study. Of course, limited intake of Pi is difficult to achieve, because significant restrictions are unfeasible since a large part of foods containing Pi are proteins, which patients are forced to take in large quantity per day (17).

Generally, haemodialyzed patients are less likely to comply with dietary guidelines for Pi. This is especially the case for younger people, who have difficulty in complying for many reasons, such as eating with friends or feeling that nothing important will happen if their serum Pi is not at the desired levels. Moreover, young people often believe that they will not be harmed by high serum Pi levels, compared with other restrictions they are asked to implement, such as the case of sodium or potassium. The major reason for these issues is that young people are less educated about the Pi diet and less aware of the consequences of hyperphosphatemia (18-20).

Studies have shown that non-adherence to the guidelines when taking phosphate binders along with an inappropriate diet are the main causes of hyperphosphatemia in haemodialyzed patients (21,22). As revealed by one study, < 25% of patients comply with the pharmaceutical and dietary instructions (23), perhaps because of their frequent gastrointestinal side effects. We believe that most patients followed the dietary guidelines, which contributed significantly to the generally low Pi levels in our patients (47% had Pi < 4.6 mg/dl). In one review, 22-74% did not comply with the guidelines regarding the use of phosphate binders, which might be associated with psychological factors and lack of social support for them (24). However, another study found higher percentages of non-compliant patients (87%) concerning phosphate binders intake (16).

Younger patients are more likely to be non-adherent to phosphate binders (24-27) because they probably prioritize other health-related activities (28) or because they may report non-compliance more easily, compared with elderly patients (24).

Since clearance plays a critical role in the regulation of serum Pi, HD removes less Pi than on-line hemodiafiltration. Specifically, each session removes 700-1000 mg Pi, and 25% of this amount is removed in the first hour of the session. Although a decrease in serum Pi levels is observed in the first two hours (29), the main role is played by the duration of the session. Thus, Pi is a small molecule. Since it is coated with water molecules (making it a medium-sized molecule), it cannot easily pass through membranes because its hydrated form makes it a large radius molecule. Our patients did not have any problems with reduced attributable clearance.

When a Urea Reduction Rat of < 65% is established, the problem is solved immediately, in our unit by correcting the fistula or the central catheter not functioning satisfactorily and by prolonging the session duration, after enhancement of the filter surface, blood and dialysate flow and anticoagulation.

A study sampled 80 Emirate haemodialyzed patients and found that age was negatively associated with hyperphosphatemia in younger people (30), which was confirmed by this and other studies (31,32). Owaki et al. studied 1492 haemodialyzed patients and found a negative correlation between age and serum Pi levels (p < 0.01) (33). Bellasi et al. sampled 1716 patients with chronic kidney disease (CKD) of various stages and found that elevated Pi levels were positively correlated with young age (34).

Thus, younger patients were those who failed to adhere to dietary guidelines for low-Pi foods compared with elders (35); whereas another study showed that good adherence played an important role in achieving good Pi level among patients with ESRD at any age (36). However, a study found that adherence to dietary guidelines among haemodialyzed patients was unrelated to serum Pi levels (37). Thus, the lowest Pi levels found in the elderly patients were due to their reduced tubular reabsorption compared with the younger ones (38).

Pi levels among haemodialyzed patients were found to be higher in women (30,31,35,39,40), although our study did not agree with this evidence. The reason for this is unclear; this may be that oestrogen reduces PTH transcription and vitamin D activation, as well as increases fibroblast growth factor (FGF-23) levels, as found experimentally by one study (41). All of these factors contribute to the regulation of tubular reabsorption of Pi, which shows that decreased urinary renal excretion is found in women compared with men.

Bellasi et al. found that Pi levels were positively correlated to the presence of diabetes mellitus (34). Among the patients with elevated Pi levels, 29.4% had diabetes mellitus. In comparison, of those with low Pi levels, 20.8% had diabetes mellitus (42), which was confirmed by another study (25). However, we found that the elderly patients (Group B) who had more diabetics had lower Pi levels than the younger ones (Group A). Younger patients in our study were also found to have higher serum PTH levels, which was explained by their higher serum Pi levels, as others have found (43,44).

The 50% of haemodialyzed patients with serum Pi levels are within the recommended levels (< 5.2 mg/dl) (19,45,46). In Groups A and B, one-year mean values in our patients had levels < 5.2±1.4 mg/dl, implying that special attention was paid to the regulation of their serum Pi, as agreed by one study (47). Specifically, 47% of our patients have levels below 4.6 mg/dl (48), which are considered normal, regardless of their age. The 2003 K/DOQI clinical practice guidelines recommend that serum Pi levels in haemodialyzed patients are good in the range of 3.5-5.5 mg/dl and the Ca²⁺xPi product of < 55 m²/ml² (49). In conclusion, a large percentage of our patients have satisfactory serum Pi levels, and the younger ones have less satisfactory serum Pi levels, compared with the elderly. Diabetics had lower serum Pi levels.

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