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Phosphate Levels and Blood Pressure in Incident Hemodialysis Patients: A Longitudinal Study

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Abstract

An elevated serum phosphate level in hemodialysis patients has been associated with mineral deposition in blood vessels. We studied a possible physiologic consequence of hyperphosphatemia by examining the relation between serum phosphate levels and blood pressure in 707 incident hemodialysis patients from 75 clinics who were enrolled in a prospective cohort study. We conducted cross-sectional and longitudinal multiple linear regression analyses, adjusting for demographics, medical history and laboratory factors. In cross-sectional analyses at baseline, elevated serum phosphate was associated with higher pre-dialysis systolic blood pressure (SBP) and pulse pressure (PP) at the start of dialysis; each 1 mg/dL higher phosphate level was associated with 1.77 mmHg higher SBP. In multivariable adjusted longitudinal analyses, for each 1 mg/dL higher serum phosphate at baseline, SBP was higher at: 3 months, 1.36 mmHg ($p=0.005$); 6 months, 1.13 mmHg ($p=0.035$); 12 months, 1.65 mmHg ($p=0.008$); 18 months, 1.44 mmHg ($p=0.031$); and 27 months, 2.54 mmHg ($p=0.002$); and PP was higher at: 3 months, 0.80 mmHg ($p=0.027$); 6 months, 0.91 mmHg ($p=0.022$); 12 months, 1.45 mmHg ($p<0.001$); 18 months, 1.06 mmHg ($p=0.026$); and 27 months, 1.37 mmHg ($p=0.020$). This study suggests that serum phosphate level is strongly and independently associated with blood pressure in hemodialysis patients. The effect of rigorous control of serum phosphate levels on arterial stiffness and blood pressure should be studied in clinical trials.

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Keywords

phosphate; blood pressure; hemodialysis

INTRODUCTION

Hypertension is common in hemodialysis patients. Despite the benefits of blood pressure medications and dialysis, more than half (50–60%; up to 86%) of hemodialysis patients still have hypertension (1–3). Hypertension has been shown to be associated with higher risk of cardiovascular mortality in hemodialysis patients (4). There are many possible mechanisms for hypertension-related mortality in dialysis patients, including activation of renin-angiotensin system, calcification of the arterial tree, and endothelium-derived vasoconstrictors (5).

Recent animal studies suggested that serum phosphate is an independent predictor of vascular calcification (6). High levels of phosphate promote calcium deposition in aortic smooth muscle cells in time- and dose-dependent manner (6). Vascular deposition could have physiologic consequences on blood pressure by affecting vessel compliance (7;8). However, there is conflicting evidence of an association of elevated calcium-phosphate product and vascular calcification (9).

Effective phosphate removal by hemodialysis is complicated by phosphate's biphasic elimination from the body (rebound of plasma level after reaching nadir)(8;10), and restriction of dietary phosphorus intake can be complicated by protein malnutrition (11). Thus, the majority of patients undergoing dialysis and dietary phosphorus restriction still have hyperphosphatemia. Our hypothesis was that hyperphosphatemia in dialysis patients can potentially lead to vascular wall stiffness and resistant hypertension. To our knowledge, no clinical trial has examined the relationship between serum phosphate and blood pressure. We therefore tested, in a national cohort of incident hemodialysis patients, the hypothesis that hemodialysis patients exposed to high levels of serum phosphate would have higher blood pressure levels early in dialysis and over time.

METHODS**Study Design and Subjects**

The study patients were a subpopulation of patients who participated in the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study (12) treated at Dialysis Clinic Inc. (DCI, Nashville, TN) clinics whose laboratory measures were all performed at a single central laboratory. From October 1995 to June 1998, 1041 patients were enrolled from 81 dialysis clinics in 19 states (12). These included clinics associated with DCI, New Haven CAPD (New Haven, CT), and the Hospital of Saint Raphael (New Haven, CT). All patients were incident kidney failure patients who were starting outpatient dialysis and who were older than 17 years of age. Patients were enrolled a median of 45 days after the start of dialysis (98% within 4 months). CHOICE study patients were similar with respect to age, sex, and race to the contemporary (1997) United States (U.S.) dialysis population (13).

The participants for this hyperphosphatemia and blood pressure substudy were limited to patients at DCI clinics who used hemodialysis (HD) as their initial renal replacement modality ($n=739$) to minimize differences in phosphate clearance that may occur with different modalities and in phosphate assays across dialysis treatment sites. A total of 707 of these patients treated at 75 clinics had data on both phosphate and blood pressure at baseline. All patients provided informed consent. The Johns Hopkins University School of Medicine Institutional Review Board and the review boards for the clinical centers approved the protocol.

Data Collection

The baseline data represent the average data 45 days before and after enrollment; this window exclusively captured data after dialysis initiation for all but one patient. Serum phosphate was measured by spectrophotometric method using phosphomolybdate at the DCI central laboratory and values were averaged over 90-day periods around baseline and every 3-month follow-up period thereafter. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with the participants in the sitting position, before and after each dialysis session. Pulse pressure (PP) was calculated as the difference between SBP and DBP. Predialysis values were used for analysis.

We collected data on several potential confounders. We collected data regarding patient demographics (age, gender, and race) and socioeconomic status (education, employment, and marital status) from a baseline self-report questionnaire. A trained research nurse completed the Index of Coexistent Disease (ICED), a measure of the severity of 19 comorbid diseases, at enrollment by reviewing medical records (14;15). The ICED score was categorized as mild (0 or 1), moderate (2), or severe (3). We coded the prevalence of cardiovascular disease (CVD) as positive if the patient had a history of coronary artery disease, myocardial infarction, cerebrovascular disease, peripheral vascular disease or transient ischemic attack at enrollment. We divided the timing of first referral to a nephrologist relative to the initiation of chronic hemodialysis into three categories (less than 4 months, 4–12 months and more than 12 months (16)). We defined non-adherence as missing more than 3% of hemodialysis sessions (17). Participants were considered to be ever smokers or non-smokers based on self-reported questionnaire. Medication information was also recorded at enrollment, including beta blocker, calcium channel blocker and ACE inhibitor use. USRDS medical evidence and claims data were used to assess injectable vitamin D (calcitriol) use.

In addition to the measurement of phosphate levels, laboratory data included repeated measures of serum calcium, potassium, parathyroid hormone (PTH), albumin and hemoglobin. The baseline laboratory parameters were those collected in the 3 months surrounding enrollment in the study (45 days before and 45 days after enrollment). PTH levels were measured using the Diasorin intact PTH assay (Diasorin Inc., Stillwater, MN). Serum calcium levels reported in the study were adjusted for hypoalbuminemia using the following formula: adjusted calcium = measured calcium + $((4.0 - \text{serum albumin in g/dL}) \times 0.8)$. High-sensitivity C-reactive protein (CRP) was performed on all patients with frozen serum available in the CHOICE specimen bank. For all laboratory and blood pressure variables, the average value in the 3-month period was used in the analysis when more than one measurement existed.

Statistical Analysis

Using χ^2 tests, we examined the relationship between serum phosphate levels and both patient characteristics (age, sex, race, diabetes mellitus (DM), baseline cardiovascular disease (CVD) and ICED, albumin, CRP, anti-hypertensive medication use and non-adherence) and blood pressure (SBP, DBP and PP) quartile. Confounders considered for multivariable adjustments were variables associated with both phosphate and blood pressure.

We used multiple linear regression analysis to examine the association between serum phosphate levels and blood pressure at baseline, adjusting for potential confounders and possible interactions and accounting for within clinic correlations by using fixed-effects modeling. To examine the impact of baseline and 0- to 3-month serum phosphorus levels on blood pressure, we used multiple linear regression to analyze the data up to 2 years of follow-up. We also compared the blood pressure in different follow-up periods between patients without (0%) any serum phosphate measurement greater than 5.5 mg/dl, patients with some (greater than 0%, less than 100%) serum phosphate measurements greater than 5.5 mg/dl and

patients with all (100%) of their serum phosphate measurements greater than 5.5 mg/dl during the first 3 months. A sensitivity analysis was conducted by adding possibly confounding but non-significant factors individually into the baseline and longitudinal regression models. We also examined the associations of serum calcium and calcium-phosphate product with blood pressure using a similar statistical approach. Cox proportional hazard models were used to examine the mortality using baseline serum phosphate as the independent predictor, adjusting for potential confounders. Patients were censored at transplantation or last day of follow-up (December 31, 2004). Statistical analyses were performed using STATA software, version 9.0 (Stata Corporation, College Station, TX). A two-sided P-value <0.05 was considered statistically significant.

RESULTS

Characteristics of Study Cohort

Among the 739 incident hemodialysis patients, 707 patients had complete data on BP and phosphate at baseline (Table 1). Patient mean age was 58.9 ± 16.7 years, mean BMI was 27.4 ± 7.5 , mean albumin level was 3.6 ± 0.3 g/dl, and mean hemoglobin level was 10.6 ± 9.2 mg/dl. The median value of CRP was 0.39 mg/dl (inter-quartile range (IQR) 0.18–0.98 mg/dl) and the median value for PTH was 156.5 pg/dl (IQR 5.5–1654 pg/dl). Patients in the highest quartile of serum phosphate were less likely to be African-American, older than 65 years or to have been referred to a nephrologist less than 4 months prior to starting hemodialysis, and they were more likely to be ever-smokers and overweight (Table 1). Median length of follow-up for blood pressure was 2.9 years (maximum, 7.2 years).

Association of Serum Phosphate with Blood Pressure in Cross-Sectional Analysis at Baseline

The mean $\pm$ SD number of measurements per follow-up period were 3.9 ± 2.8 for phosphate and 34.6 ± 7.6 for blood pressure. Unadjusted baseline mean SBP and DBP were greater with increasing phosphate quartile, $p=0.002$ and $p<0.001$, respectively (Figure 1). Unadjusted baseline mean PP was not statistically significantly greater with increasing phosphate quartile ($p=0.11$).

After adjustment for demographics, laboratory and clinical variables, greater serum phosphorus quartile was significantly associated with higher SBP ($p=0.003$), and PP ($p=0.003$) but not DBP ($p=0.09$) (Table 2). For each 1 mg/dL higher serum phosphate, SBP was greater by 1.77 mmHg, DBP by 0.44 mmHg and PP by 1.32 mmHg (Table 2). When patients were stratified into subgroups, serum phosphate was associated with baseline SBP in patients without diabetes, with ICED score of 2, and in all patients regardless of age, race, gender, and CVD history status. Interaction terms in regression analyses of all patients were not statistically significant for any of the patient subgroups. The patterns were generally similar for baseline DBP and PP (Table 2).

Association of Serum Phosphate and Mortality Adjusted for Blood Pressure at Baseline

Serum phosphate was an independent predictor for mortality adjusted for age, sex, race, baseline modality, smoking, BMI, ICED, diabetes, CVD, CRP, IL-6, albumin, hemoglobin, and PTH (Hazard ratio (HR)) 1.66, 95%CI :1.10, 2.51). After adjustment for SBP, the HR was 1.71 (1.08, 2.71); after adjustment for DBP, the HR was 1.68 (1.06, 2.65); and after adjustment for PP, the HR was 1.71 (1.08, 2.70). There was no association between baseline BP measurements and all-cause mortality with this set of adjusters, including phosphate (data not shown).

Association of Serum Phosphate at Baseline with Blood Pressure Over Time

There was a significant association between baseline serum phosphate and blood pressure at different follow-up intervals. For each 1 mg/dl higher serum phosphate at baseline, SBP was 1.36 mmHg higher ($p<0.005$), DBP was 0.63 mmHg higher ($p=0.010$) and PP was 0.80 mmHg higher in PP ($p=0.027$) at 3-month follow-up (Table 3). Similar associations were seen in SBP and PP in the subsequent follow-up periods.

In order to adjust for potential confounding of inter-individual differences in blood pressure by pre- and post-dialysis changes in extracellular volume, we conducted similar analyses using the average of pre- and post-dialysis blood pressure at baseline and each follow-up. There was still a significant association between baseline serum phosphate and SBP, PP at baseline and every 3 months until the 27-month follow-up ($P<0.05$).

Association of Average Serum Phosphate from 0 to 3 months with Blood Pressure at Different Follow-up Intervals

There was a stronger association between the average of 0 to 3 months serum phosphate and blood pressure. For each 0- to 3-month average 1 mg/dl higher serum phosphate, SBP was 1.65 mmHg higher ($p=0.001$), DBP was 0.74 mmHg higher ($p=0.005$) and PP was 1.03 mmHg higher in PP ($p=0.007$) at 3-month follow-up (Table 4). Similar associations were seen in SBP, DBP and PP in most of the subsequent follow-up periods.

Association between High Serum Phosphate Measurements from 0 to 3 Months and Blood Pressure at Different Follow-up Periods

Compared to patients without any serum phosphate level above 5.5 mg/dl, patients with some measurements greater than 5.5 mg/dl had significantly higher SBP in most of the follow-up periods ($p<0.05$). Patients with all measurements higher than 5.5 mg/dl had significantly higher SBP in all follow-up intervals and significantly higher PP in most of the follow-up periods ($p<0.05$) (Table 5).

Serum Calcium, Calcium-Phosphate Product and Blood Pressure

We performed similar analyses with serum calcium and the calcium-phosphorous (CaP) product data. There was no significant association between serum calcium level and blood pressure, at baseline or longitudinally (data not shown). There was a statistically significant association between calcium-phosphate product and both systolic and pulse blood pressure at baseline and longitudinally, but the magnitude of the association was one-tenth of the association between serum phosphate and blood pressure (data not shown).

Sensitivity Analyses

We also conducted analyses of the cross-sectional and longitudinal relationship between blood pressure and serum phosphate in which we added smoking, time of nephrology referral, BMI, calcium, potassium, calcium phosphate product, PTH and baseline vitamin D use as covariates in the adjusted regression analysis; the magnitude of change in SBP results decreased slightly, but remained statistically significant in all sensitivity models. For example, β for phosphate adjusting for referral time was +1.68, $p=0.004$; the β for phosphate adjusting for smoking was +1.74, $p=0.001$; the β for phosphate adjusting for potassium was +1.70, $p=0.02$; the β for phosphate adjusting for vitamin D use was +1.82, $p=0.02$. We also conducted baseline and longitudinal analyses in which we added dialysis adequacy (Kt/V) as a covariate; the results did not appreciably change ($\beta=1.92$, $p=0.002$ for phosphate). The longitudinal sensitivity analyses yielded similar results, except for the model adding vitamin D, which failed to show statistical significance (data not shown). Vitamin D use information was only available in 346 patients at baseline, in 321 patients at 3 months, and in 301 patients at 6 months.

DISCUSSION

This prospective cohort study in incident hemodialysis patients showed that serum phosphorus at the beginning of dialysis was strongly and independently associated with SBP, DBP and PP. This association was seen both cross-sectionally and over time. In addition, it showed that the average serum phosphate from baseline to 3 months was associated with a subsequently higher SBP, DBP and PP. The magnitude of these associations was greater for SBP and PP than for DBP. We adjusted for all potential confounders in this study, including anti-hypertensive medication use (beta-blocker, Calcium channel blocker or angiotensin converting enzyme (ACE) inhibitor), patient demographics (age, sex, race), medical history (ICED score, DM, baseline CVD), laboratory values (albumin, log(CRP)) and dialysis non-adherence. Our analyses with calcium and CaP product data indicated that serum phosphate rather than calcium was associated with blood pressure at baseline and over time. A likely mechanism is that hyperphosphatemia leads to mineral deposition in the vascular wall (i.e., metastatic calcification) and this leads to arterial wall stiffness and vessel non-distensability (18;19).

The effect of phosphate concentration on vascular calcification is supported by Raggi and co-workers. (20), who found that the extent of arterial calcification in adult HD patients was associated with age, male sex, white race, diabetes, dialysis therapy, higher serum calcium and higher serum phosphate concentration. In another study, serum phosphate concentration was higher in young HD patients with coronary calcification than in those without (21).

The vascular calcification process in hyperphosphatemia is similar to that of normal skeletal mineralization (22). Increasing phosphate concentration in vascular smooth muscle cell culture results in a dose-dependent increase in intracellular phosphate via a type III sodium-phosphate cotransporter (6;23). This ultimately increases bone-related protein expression of markers such as core-binding factor alpha-1 (cbfa-1) and osteocalcin. Animal models confirm this phenotypic change in vascular smooth muscle cells and human pathologic studies in ESRD substantiate the expression of bone-related proteins in areas of vascular calcification (24;25). Hyperphosphatemia is also an independent predictor of left ventricular hypertrophy (LVH) (26;27), likely due to the decreased vascular compliance and increased afterload. Short daily hemodialysis significantly decreased serum phosphate level at the end of six months, compared to conventional hemodialysis, and SBP, PP, and LVH were all found to be significantly reduced in patients receiving short daily hemodialysis (27).

Our study is one of the first to address the associations of elevated serum phosphate level and higher blood pressures over time. The association of elevated phosphate and high blood pressure persisted even after 2 years. This suggests the persistence of arterial wall stiffness as the result of baseline hyperphosphatemia. Klassen and colleagues (28) reported that phosphate concentration was directly associated with pulse pressure, which was a strong predictor of 1-year mortality. Melamed et al. (29) found that patients whose phosphate levels were high at baseline but subsequently decreased significantly by 6 months had a higher mortality relative to those whose levels were low at both time points. The National Kidney Foundation recommends maintaining a serum phosphate concentration between 3.5 and 5.5 mg/dl in stage 5 chronic kidney disease patients (HD patients) (30). Our results suggest that even if serum phosphate level can be lowered in a short period of time, the vascular calcification from hyperphosphatemia may require a longer time to correct.

Pulse pressure is the difference between systolic and diastolic blood pressure. The rise in aortic pressure from its diastolic to systolic value is determined by the compliance of the aorta as well as the ventricular stroke volume. In the arterial system, the aorta has the highest compliance, due in part to a relatively greater proportion of elastin fibers versus smooth muscle and collagen. Therefore, aortic compliance is a major determinant, along with stroke volume,

of the pulse pressure. Guerin et al. (31) reported aortic pulse velocity has the highest sensitivity and specificity in predicting cardiovascular death in ESRD patients. Klassen et al. (28) reported that an increment of 10 mmHg in PP was associated with 12% increase in mortality in HD patients.

Our results suggested that baseline serum phosphate is an independent predictor of all-cause mortality, even adjusted for baseline blood pressure. Higher mortality could be mediated not by subsequent vascular calcification from hyperphosphatemia but through other mechanisms (e.g. fibroblast growth factor-23 levels in hyperphosphatemia) (32). Our study did not show that baseline blood pressure is a significant predictor for mortality, although Klassen and co-workers demonstrated this relationship in hemodialysis patients (28). Our results reinforce the importance of serum phosphate control in reducing all-cause mortality in hemodialysis patients.

One potential confounding factor for hyperphosphatemia is non-adherence to HD. Patients who are non-adherent to HD may also be non-adherent to their anti-hypertensives. Leggat and colleagues (33) suggested that skipping HD sessions could be considered with other non-adherent behaviors, such as high interdialytic weight gain, greater serum potassium and phosphate levels. Unruh and colleagues (17) reported that skipping 3% of HD sessions is associated with 69% increase in risk of death. We tried to eliminate non-adherence as a cause of hyperphosphatemia by adjusting for non-adherence to HD and for serum potassium in our study.

One strength of our study is repetitive blood pressure measurements. There was an average of 35 pre- and post-dialysis BP measurements in each patient during each follow-up period. The average BP value in this study is a good reflection of the BP in these HD patients although there is generally a big variation of BP in this population. We also used the average of pre- and post-dialysis BP to eliminate potential inter-individual differences in changes of extracellular volume. A similar but even stronger association was found.

This study has several limitations. First, this is an observational study. We cannot establish causality although several features of our study design and results are suggestive of a causal relation, including temporality, strength of the association, the graded nature of the association and biologic plausibility. Second, we did not have data on arterial wall stiffness to examine the mechanism for the observed associations. Although pulse pressure may be a surrogate measure of the arterial wall stiffness, Doppler measurement would have provided more accurate information about arterial wall compliance. Third, there may be residual confounding. For example, we only had information on baseline vitamin D use for 346 patients in the cohort and these data did not include dose or frequency of administration. The association between blood pressure (SBP & PP) and serum phosphate level was present at baseline when we adjusted for vitamin D use, but disappeared at follow-up intervals. We suspect the lack of association in follow-up is due to the smaller sample size over time. Finally, we did not have complete data on calcium-containing and non-calcium-containing phosphate binder use.

In summary, this study found that serum phosphorus is strongly and independently associated with systolic blood pressure and pulse pressure in the early months of dialysis therapy and up to 27 months later. The role of hyperphosphatemia in vascular calcification and arterial stiffness still needs to be further clarified. Studies relating phosphate level to direct measurements of arterial wall stiffness and examining whether lowering serum phosphate will decrease vascular calcification and blood pressure would be very useful.

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REFERENCES

1. Agarwal R, Nissenson AR, Battle D, Coyne DW, Trout JR, Warnock DG. Prevalence, treatment, and control of hypertension in chronic hemodialysis patients in the United States. *Am J Med* 2003;115:291–297. [PubMed: 12967694]
2. HCFA-1995. Annual Report. ESRD core indicators project. Opportunities to improve care for adult in-center hemodialysis patients. 1-19-1996.
3. Rahman M, Dixit A, Donley V, Gupta S, Hanslik T, Lacson E, Ogundipe A, Weigel K, Smith MC. Factors associated with inadequate blood pressure control in hypertensive hemodialysis patients. *Am J Kidney Dis* 1999;33:498–506. [PubMed: 10070914]
4. Zager PG, Nikolic J, Brown RH, Campbell MA, Hunt WC, Peterson D, Van Stone J, Levey A, Meyer KB, Klag MJ, Johnson HK, Clark E, Sadler JH, Teredesai P. Medical Directors of Dialysis Clinic. "U" curve association of blood pressure and mortality in hemodialysis patients. *Inc. Kidney Int* 1998;54:561–569.
5. Mailloux LU. Hypertension in chronic renal failure and ESRD: prevalence, pathophysiology, and outcomes. *Semin Nephrol* 2001;21:146–156. [PubMed: 11245777]
6. Giachelli CM, Jono S, Shioi A, Nishizawa Y, Mori K, Morii H. Vascular calcification and inorganic phosphate. *Am J Kidney Dis* 2001;38:S34–S37. [PubMed: 11576919]
7. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol* 2004;15:2208–2218. [PubMed: 15284307]
8. Schucker JJ, Ward KE. Hyperphosphatemia and phosphate binders. *Am J Health Syst Pharm* 2005;62:2355–2361. [PubMed: 16278327]
9. O'Neill WC. The fallacy of the calcium-phosphorus product. *Kidney Int* 2007;72:792–796. [PubMed: 17609689]
10. Spalding EM, Chamney PW, Farrington K. Phosphate kinetics during hemodialysis: Evidence for biphasic regulation. *Kidney Int* 2002;61:655–667. [PubMed: 11849409]
11. Lorenzo SV, Torres RA. Management of hyperphosphatemia in dialysis patients: role of phosphate binders in the elderly. *Drugs Aging* 2004;21:153–165. [PubMed: 14979734]
12. Powe NR, Klag MJ, Sadler JH, et al. Choices for Healthy Outcomes in Caring for End Stage Renal Disease. *Semin Dial* 1996;9:9–11.
13. U.S. Renal Data System. U.S. Renal Data System 1999 annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD: National Institute of Health, National Institute of Diabetes and Digestive and Kidney Disease; 1999.
14. Greenfield S, Sullivan L, Silliman RA, Dukes K, Kaplan SH. Principles and practice of case mix adjustment: applications to end-stage renal disease. *Am J Kidney Dis* 1994;24:298–307. [PubMed: 8048437]
15. Miskulin DC, Meyer KB, Athienites NV, Martin AA, Terrin N, Marsh JV, Fink NE, Coresh J, Powe NR, Klag MJ, Levey AS. Comorbidity and other factors associated with modality selection in incident dialysis patients: the CHOICE Study. Choices for Phosphate and Blood Pressure Healthy Outcomes in Caring for End-Stage Renal Disease. *Am J Kidney Dis* 2002;39:324–336. [PubMed: 11840373]

16. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag MJ, Levey AS, Powe NR. The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med* 2002;137:479–486. [PubMed: 12230348]
17. Unruh ML, Evans IV, Fink NE, Powe NR, Meyer KB. Skipped treatments, markers of nutritional nonadherence, and survival among incident hemodialysis patients. *Am J Kidney Dis* 2005;46:1107–1116. [PubMed: 16310577]
18. Delmez JA, Slatopolsky E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. *Am J Kidney Dis* 1992;19:303–317. [PubMed: 1562018]
19. Huting J. Mitral valve calcification as an index of left ventricular dysfunction in patients with end-stage renal disease on peritoneal dialysis. *Chest* 1994;105:383–388. [PubMed: 8306733]
20. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, Chertow GM. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002;39:695–701. [PubMed: 11849871]
21. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, Elashoff RM, Salusky IB. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;342:1478–1483. [PubMed: 10816185]
22. Davies MR, Hruska KA. Pathophysiological mechanisms of vascular calcification in end-stage renal disease. *Kidney Int* 2001;60:472–479. [PubMed: 11473629]
23. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM. Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res* 2000;87:E10–E17. [PubMed: 11009570]
24. Moe SM, O'Neill KD, Duan D, Ahmed S, Chen NX, Leapman SB, Fineberg N, Kopecky K. Medial artery calcification in ESRD patients is associated with deposition of bone matrix proteins. *Kidney Int* 2002;61:638–647. [PubMed: 11849407]
25. Shioi A, Taniwaki H, Jono S, Okuno Y, Koyama H, Mori K, Nishizawa Y. Monckeberg's medial sclerosis and inorganic phosphate in uremia. *Am J Kidney Dis* 2001;38:S47–S49. [PubMed: 11576921]
26. Achinger SG, Ayus JC. Left Ventricular Hypertrophy: Is Hyperphosphatemia among Dialysis Patients a Risk Factor? *J Am Soc Nephrol* 2006;17:S255–S261. [PubMed: 17130271]
27. Ayus JC, Mizani MR, Achinger SG, Thadhani R, Go AS, Lee S. Effects of short daily versus conventional hemodialysis on left ventricular hypertrophy and inflammatory markers: a prospective, controlled study. *J Am Soc Nephrol* 2005;16:2778–2788. [PubMed: 16033855]
28. Klassen PS, Lowrie EG, Reddan DN, DeLong ER, Coladonato JA, Szczec LA, Lazarus JM, Owen WF Jr. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. *JAMA* 2002;287:1548–1555. [PubMed: 11911757]
29. Melamed ML, Eustace JA, Plantinga L, Jaar BG, Fink NE, Coresh J, Klag MJ, Powe NR. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. *Kidney Int* 2006;70:351–357. [PubMed: 16738536]
30. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003;42:S1–S201. [PubMed: 14520607]
31. Guerin AP, London GM, Marchais SJ, Metivier F. Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant* 2000;15:1014–1021. [PubMed: 10862640]
32. Stubbs JR, Liu S, Tang W, Zhou J, Wang Y, Yao X, Quarles LD. Role of hyperphosphatemia and 1,25-dihydroxyvitamin D in vascular calcification and mortality in fibroblastic growth factor 23 null mice. *J Am Soc Nephrol* 2007;18:2116–2124. [PubMed: 17554146]
33. Leggat JE Jr, Orzol SM, Hulbert-Shearon TE, Golper TA, Jones CA, Held PJ, Port FK. Noncompliance in hemodialysis: predictors and survival analysis. *Am J Kidney Dis* 1998;32:139–145. [PubMed: 9669435]

Figure 1.

Mean ± 1.96 SE (diamond) and ± 1.96 SD (bars) of systolic (SBP), diastolic (DBP) and pulse pressure (PP) by baseline mean serum phosphate quartiles ($n=707$). P values from ANOVA are shown below the bars. SBP in Quartile 1 is significantly different from Quartile 2 ($p=0.002$) and 3 ($p=0.014$). DBP in Quartile 1 is significantly different from Quartile 2 ($p=0.009$) and 3 ($p<0.001$).

Table 1
Baseline characteristics of hemodialysis patients by serum phosphate quartile at baseline (n=707)

Characteristic	Serum phosphate (mg/dl)								p value*
	Quartile1 <4.42		Quartile 2 4.42-5.21		Quartile3 5.21-6.07		Quartile 4 >6.07		
	n	%	n	%	n	%	n	%	
	178	100	175	100	177	100	177	100	
Demographics									
Age>65 years	95	53	72	41	63	36	49	28	<0.001
Female	87	49	81	46	79	45	78	44	0.80
African American	64	36	60	34	51	29	43	24	0.007
> High school grad	57	34	49	29	57	34	58	34	0.67
Medical History									
Ever smoked	85	49	109	64	100	58	120	70	0.003
Baseline cardiovascular disease	113	63	102	58	110	62	93	53	0.15
Diabetes mellitus	86	48	97	55	107	60	101	57	0.13
ICED score 2	68	38	61	35	60	34	79	45	0.53
ICED score 3	56	31	59	34	63	36	47	27	
Late referral < 4 mo	48	34	58	39	51	34	32	23	0.030
Beta-blocker use	43	24	36	21	45	25	44	25	0.71
ACE inhibitor use	45	25	43	25	57	32	50	28	0.36
Ca channel blocker use	100	61	111	63	104	59	107	60	0.84
Exam and Labs									
Body mass index >25 kg/m ²	80	48	94	58	105	63	100	60	0.030
C Reactive Protein>0.4 mg/dl	88	52	90	53	77	46	73	44	0.27
Albumin >3.7 mg/dl	85	48	85	49	77	44	97	55	0.18
Hemoglobin >10.8 g/dl	85	48	85	49	78	44	76	43	0.68
Parathyroid hormone >160 ps/dl	57	41	67	50	69	52	75	56	0.08

* P Value is from χ^2 tests for each categorical variable and serum phosphate quartiles.

Table 2

Cross-sectional association of baseline serum phosphate (per 1 mg/dl) with baseline systolic, diastolic and pulse blood pressure in all patients and patient subgroups, adjusted for patient characteristics in the subpopulation of patients with complete data on all variables (n=669)

All patients	N	Systolic blood pressure		Diastolic blood pressure		Pulse pressure	
		β*	P value	β*	P value	β*	P value
By phosphate quartile							
Quartile 1 (<4.42 mg/dl)	169	Reference (mean SBP=147.27 mmHg)		Reference (mean DBP =76.62 mmHg)		Reference (mean PP =70.66 mmHg)	
Quartile 2 (4.42–5.21 mg/dl)	169	+3.18	0.07	+0.65	0.45	+2.52	0.05
Quartile 3 (5.21–6.07 mg/dl)	167	+5.52	0.002	+1.34	0.12	+4.14	0.002
Quartile 4 (>6.07 mg/dl)	164	+5.18	0.006	+1.37	0.13	+3.81	0.006
p value (test of trend)		0.003		0.09		0.003	
For 1 mg/dL higher of phosphate							
All Patients	669	+1.77	0.001	+0.44	0.09	+1.32	0.001
Patient subgroup							
Diabetes mellitus [#]	Yes	+1.27	0.09	+0.50	0.14	+0.73	0.18
	No	+2.41	0.003	+0.51	0.22	+1.97	0.001
Age [#]	>65	+2.19	0.035	+0.88	0.06	+1.26	0.10
	<65	+1.43	0.019	+0.69	0.036	+0.74	0.10
Race [#]	White	+2.37	0.001	+0.77	0.016	+1.61	0.003
	African American	+0.76	0.42	−0.03	0.10	+0.74	0.28
	Other	+1.21	0.79	+2.00	0.36	−0.26	0.81
Gender [#]	Female	+1.60	0.06	+0.02	0.96	+1.54	0.017
	Male	+1.69	0.024	+0.70	0.06	+1.00	0.07
Baseline Cardiovascular disease [#]	Yes	+1.27	0.10	+0.25	0.48	+1.02	0.07
	No	+1.88	0.020	+0.28	0.48	+1.59	0.010
ICED score [#]	0 or 1	+1.29	0.21	+0.47	0.38	+0.84	0.29
	2	+2.06	0.012	+0.37	0.33	+1.66	0.009
	3	+1.73	0.13	+0.37	0.49	+1.37	0.08

* β is mmHg higher of blood pressure per 1 mg/dl higher serum phosphate at baseline adjusted for all characteristics in table as well as serum albumin, log(C-reactive protein), dialysis non-adherence, and any β -blocker, Ca channel blocker or ACE inhibitor use.

[#] Adjusted for the above patient characteristics except for the indicated variable.

Table 3
Association of 1 mg/dl higher in serum phosphate at baseline with blood pressure at different follow-up intervals, adjusted for patient characteristics.

Blood Pressure Follow-up	Systolic Blood Pressure			Diastolic Blood Pressure			Pulse Pressure		
	N	β *	P value	B*	P value	β *	P Value		
3 months	651	+1.36	0.005	+0.63	0.010	+0.80	0.027		
6 months	612	+1.13	0.035	+0.27	0.31	+0.91	0.022		
9 months	570	+0.87	0.14	+0.14	0.62	+0.77	0.08		
12 months	526	+1.65	0.008	+0.22	0.47	+1.45	0.001		
15 months	495	+1.48	0.028	+0.41	0.22	+1.08	0.024		
18 months	470	+1.44	0.031	+0.39	0.27	+1.06	0.026		
21 months	440	+1.08	0.13	+0.42	0.24	+0.65	0.21		
24 months	409	+1.54	0.05	+0.63	0.11	+0.87	0.13		
27 months	377	+2.54	0.002	+1.14	0.005	+1.37	0.020		

* β is mmHg higher of blood pressure per 1 mg/dl higher serum phosphate at baseline adjusted for age, sex, race, baseline blood pressure, ICED score, albumin, log(C-reactive protein), DM, baseline CVD, dialysis non-adherence, and any β -blocker, Ca channel blocker or ACE inhibitor use.

Association of 1 mg/dl higher average serum phosphate measurements up to 3 months with blood pressure at different follow-up intervals, adjusted for patient characteristics.

Blood Pressure Follow-up	Systolic Blood Pressure			Diastolic Blood Pressure			Pulse Pressure		
	N	B*	P value	B*	P value		β*	P value	
3 months	651	+1.65	0.001	+0.74	0.005		+1.03	0.007	
6 months	612	+1.37	0.016	+0.81	<0.001		+1.06	0.011	
9 months	570	+1.20	0.06	+0.32	0.27		+0.96	0.038	
12 months	526	+1.91	0.003	+0.55	0.09		+1.42	0.002	
15 months	495	+1.71	0.012	+0.66	0.05		+1.13	0.019	
18 months	470	+1.91	0.005	+0.64	0.07		+1.33	0.006	
21 months	440	+1.75	0.016	+0.79	0.028		+1.00	0.06	
24 months	409	+2.00	0.014	+0.95	0.019		+1.06	0.07	
27 months	377	+2.33	0.006	+1.08	0.011		+1.31	0.030	

* β is mmHg increase of blood pressure per 1 mg/dl higher serum phosphate at baseline adjusted for age, sex, race, baseline blood pressure, ICED score, albumin, log(C-reactive protein), DM, baseline CVD, dialysis non-adherence, and any β-blocker, Ca channel blocker or ACE inhibitor use.

Table 5

Association of different percentage of serum phosphate measurements greater than 5.5 mg/dl from 0 to 3 months with blood pressure at different follow-up intervals using 0% of serum phosphate >5.5mg/dl as reference, adjusted for patient characteristics.

Blood Pressure Follow-up	% of measurements >5.5 mg/dl+	n	Systolic Blood Pressure			Diastolic Blood Pressure			Pulse Pressure		
			β	p value	β	p value	β	p value	β	p value	p value
3 months	none	129	0	ref	0	ref	0	ref	0	ref	ref
	some	463	+4.16	0.005	+2.19	0.003	+2.04	0.06	+2.04	0.06	0.06
	all	59	+5.72	0.018	+2.47	0.042	+3.48	0.05	+3.48	0.05	0.05
6 months	none	118	0	ref	0	ref	0	ref	0	ref	ref
	some	441	+2.31	0.15	+1.16	0.15	+1.11	0.35	+1.11	0.35	0.35
	all	53	+6.46	0.016	+0.93	0.49	+5.65	0.004	+5.65	0.004	0.004
12 months	none	108	0	ref	0	ref	0	ref	0	ref	ref
	some	374	+4.27	0.017	+1.79	0.048	+2.42	0.06	+2.42	0.06	0.06
	all	44	+8.50	0.005	+1.88	0.22	+6.68	0.002	+6.68	0.002	0.002
18 months	none	99	0	ref	0	ref	0	ref	0	ref	ref
	some	334	+4.23	0.025	+1.03	0.30	+3.02	0.025	+3.02	0.025	0.025
	all	37	+5.05	0.13	+1.11	0.52	+3.74	0.11	+3.74	0.11	0.11
24 months	none	85	0	ref	0	ref	0	ref	0	ref	ref
	some	291	+4.57	0.036	+1.73	0.11	+2.38	0.12	+2.38	0.12	0.12
	all	33	+9.32	0.014	+5.27	0.005	+3.85	0.16	+3.85	0.16	0.16
27 months	none	80	0	ref	0	ref	0	ref	0	ref	ref
	some	263	+5.23	0.022	+1.52	0.19	+3.54	0.031	+3.54	0.031	0.031
	all	34	+9.28	0.015	+4.13	0.032	+4.94	0.07	+4.94	0.07	0.07

* β is mmHg increase of blood pressure comparing to the category that no phosphate measurement is above 5.5 mg/dl at 0-3 months adjusted for age, sex, race, baseline blood pressure, ICED score, albumin, log(C-reactive protein), DM, baseline CVD, dialysis non-adherence, and any β -blocker, Ca channel blocker or ACE inhibitor use.

+ none = no serum phosphate measurements >5.5 mg/dl; some = >0%, <100% of serum phosphate measurements >5.5 mg/dl; all = 100% of serum phosphate measurements >5.5 mg/dl within the first 3 months of enrollment.