NIH Public Access
Author Manuscript
Am J Kidney Dis. Author manuscript; available in PMC 2011 February 28.

Published in final edited form as:
Am J Kidney Dis. 2009 March ; 53(3): 399–407. doi:10.1053/j.ajkd.2008.07.036.

Serum Phosphorus Concentrations in the Third National Health and Nutrition Examination Survey (NHANES III)

Ian H. de Boer, MD, MS[1], **Tessa C. Rue, MS**[2], and **Bryan Kestenbaum, MD, MS**[3]

[1]Division of Nephrology, University of Washington, Seattle, WA

[2]Department of Biostatistics, University of Washington, Seattle, WA

[3]Division of Nephrology, Harborview Medical Center, University of Washington, Seattle, WA

Abstract

Background—Higher serum phosphorus concentrations within the normal laboratory range have been associated with cardiovascular events and mortality in large prospective cohort studies of individuals with and without kidney disease. Reasons for interindividual variation in steady-state serum phosphorus concentrations are largely unknown.

Study Design—Cross-sectional study.

Setting & Participants—15,513 participants in the Third National Health and Nutrition Examination Survey.

Predictors—Demographic data, dietary intake measured by means of 24-hour dietary recall and food-frequency questionnaire, and established cardiovascular risk factors.

Outcome & Measurements—Serum phosphorus concentration.

Results—Mean serum phosphorus concentrations were significantly greater in women (+0.16 mg/dL versus men; $P < 0.001$) and people of non-Hispanic black and Hispanic race/ethnicity (+0.06 and +0.07 mg/dL versus non-Hispanic white, respectively; $P < 0.001$). Dietary intakes of phosphorus and phosphorus-rich foods were associated only weakly with circulating serum phosphorus concentrations, if at all. Higher serum phosphorus levels were associated with lower calculated Framingham coronary heart disease risk scores, which are based on traditional atherosclerosis risk factors. In aggregate, demographic, nutritional, cardiovascular, and kidney function variables explained only 12% of the variation in circulating serum phosphorus concentrations.

Limitations—Results may differ with advanced kidney disease.

Conclusions—Serum phosphorus concentration is weakly related to dietary phosphorus and not related to a diverse array of phosphorus-rich foods in the general population. Factors determining serum phosphorus concentration are largely unknown. Previously observed associations of serum phosphorus concentrations with cardiovascular events are unlikely to be a result of differences in dietary intake or traditional cardiovascular risk factors.

Address correspondence to Bryan Kestenbaum, MD, MS, University of Washington, Division of Nephrology, Harborview Medical Center, Rm 10EH11, Box 359764, Seattle, WA 98104-2499. brk@u.washington.edu.

Financial Disclosure: Dr Kestenbaum reports receiving consulting fees from Shire Inc and Abbott Inc and receiving grant support from Amgen Inc.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Index Words

Phosphorus; nutritional; cardiovascular; kidney

Higher serum phosphorus levels are emerging as a novel biomarker of cardiovascular risk. In long-term dialysis patients, increased serum phosphorus concentrations consistently have been associated with arterial calcification and mortality independent of traditional atherosclerotic risk factors.[1-3] These associations intensify with higher serum phosphorus concentrations and are corroborated by experimental models that show a direct calcifying effect of phosphorus on cultured vascular smooth muscle tissue.[4,5]

Higher serum phosphorus concentrations within the normal range also have been associated with cardiovascular events and mortality in individuals with moderate chronic kidney disease and those with normal kidney function.[6-8] Of 3,368 participants in the Framingham Offspring Study without clinically apparent kidney or cardiovascular disease, each 1-mg/dL higher serum phosphorus concentration was associated with a 31% increased risk of a first major cardiovascular event, and of 4,159 participants in the Cholesterol and Recurrent Events (CARE) Study, each 1-mg/dL higher serum phosphorus concentration was associated with a 27% greater risk of all-cause mortality.[6,8]

Greater serum phosphorus concentrations may reflect a relatively atherogenic diet. Phosphorus is abundant in beef, milk, butter, cheese, and processed foods, which also contain high levels of saturated fats and cholesterol. However, dietary intake patterns may not inform circulating phosphorus levels because key regulatory hormones, urinary excretion, and cellular flux serve to maintain serum phosphorus concentrations within a narrow range.[9,10] The relationship between dietary practices and circulating phosphorus concentrations has not been fully explored in a large cohort.

Given recent prospective association of higher serum phosphorus concentrations with cardiovascular events, it is plausible that circulating phosphorus levels are intertwined with known atherosclerosis risk factors, such as hypertension, diabetes, and hyperlipidemia. However, relationships of phosphorus concentrations with traditional cardiovascular risk factors have been inconsistent in previous studies.[7,8,11]

In the present study, we examine nutritional variables and cardiovascular risk factors in relation to circulating serum phosphorus concentrations in a population-based nationally representative cohort.

Methods

Study Population

The Third National Health and Nutrition Examination Survey (NHANES III) was a population-based survey conducted from 1988 to 1994.[12] It was designed to provide national estimates of health and nutrition for the civilian noninstitutionalized population of the United States. Young children, older persons, black persons, and Mexican Americans were oversampled as part of a complex multistage sample design. A total of 16,575 participants 20 years or older were included in a mobile examination center evaluation; 15,513 of these (94%) had measurement of serum phosphorus and were included in this study. All participants granted informed consent for participation in NHANES III.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Measurement of Dietary Variables

Two validated instruments, the 24-hour dietary recall and the 1-month food-frequency questionnaire, were used to assess dietary variables.[13,14] Daily intakes of total energy, macronutrients, phosphorus, and alcohol were assessed by using 24-hour dietary recall collected through an in-person interviewer-administered dietary data collection system, as previously described.[12] The food-frequency questionnaire assessed the intake of dietary factors related to phosphorus consumed during the 1 month preceding the study visit. Dairy products included milk; yogurt and frozen yogurt; ice cream, ice milk, and milkshakes; and cheese of all types. Meat included beef; pork and ham; liver and other organ meats; bacon, sausage, and luncheon meats; and poultry of all types. Seafood included fish, shrimp, clams, oysters, crab, and lobster.

There were 1,179 participants who returned for repeated dietary assessment a median of 16 days later (range, 0 to 48 days). Repeated 24-hour dietary phosphorus correlated moderately with initial values (Pearson $\rho = 0.48$).

Measurement of Serum Phosphorus

During the mobile examination center evaluation, blood samples were centrifuged, aliquoted, and frozen to −70°C on site. Frozen samples were shipped on dry ice to central laboratories, where they were stored at −70°C until analysis.[15] Phosphorus was measured in serum using a Hitachi model 737 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). With this assay, inorganic phosphorus reacts with ammonium molybdate in an acidic solution to form ammonium phosphomolybdate, which is quantified in the UV range (340 nm) through the use of a sample-blanked end point method. Two concentrations of unassayed control materials were measured daily and used for quality control. Monthly coefficients of variation ranged from 0.6% to 1.0% within runs and 1.8% to 2.8% total.

There were 1,878 participants (12%) who returned for repeated serum phosphorus measurement after a median of 16 days (range, 0 to 48 days). Repeated phosphorus levels correlated with initial values (Pearson $\rho = 0.59$), and this correlation modestly increased when restricted to 1,161 participants who were fasting for both measurements ($\rho = 0.63$). The SD for intraindividual variation of serum phosphorus concentration over time was 0.31 mg/dL, after accounting for fasting status and time of day.

Measurement of Other Study Variables

Race/ethnicity was self-described as non-Hispanic white, non-Hispanic black, Hispanic, or other. Household income was measured as poverty income ratio. Fasting was defined as not eating within 8 hours of phlebotomy. Diabetes mellitus was defined as self-reported physician diagnosis of diabetes or use of diabetes medication (insulin or pills for diabetes). 16 Hypertension was defined as use of antihypertensive medication, systolic blood pressure of 140 mm Hg or greater, or diastolic blood pressure of 90 mm Hg or greater.17 Hyperlipidemia was defined as total cholesterol concentration of 200 mg/dL or greater (total cholesterol in mg/dL may be converted to mmol/L by multiplying by 0.02586).18 Smoking status was classified as never, former, or current based on responses to the questions “Do you currently smoke?” and “Have you smoked 100+ cigarettes?” Body mass index was classified as underweight (<18.5 kg/m^2), normal (18.5 to 24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), or obese (≥30 kg/m^2). Estimated glomerular filtration rate (GFR) was calculated from age, sex, race/ethnicity, and serum creatinine concentration using the 4-variable Modification of Diet in Renal Disease Study equation, with serum creatinine calibrated to Modification of Diet in Renal Disease Study values.19,20 Urine albumin and creatinine were measured from a single random voided urine sample, with urine albumin-

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

creatinine ratio categorized using established sex-specific thresholds.21 Serum 25-hydroxyvitamin D, a measure of vitamin D intake, was assayed using a radioimmunoassay kit (DiaSorin Inc, Stillwater, MN).

Statistical Methods

To increase the efficiency of the sampling process, NHANES III used a complex multistage sampling design.[12] Weights were assigned to account for varied rates of sampling by age and race/ethnicity and adjust for nonresponse bias (caused by people refusing to participate) and noncoverage bias (caused by people who did not live in households and therefore could not participate). We used the svy commands of STATA software, version 9.2 (Stata Corp, College Station, TX) in all analyses to account for both the sampling and weighting processes (pweight = *wtpfex6*, PSU = *sdppsu6*, strata = *sdpstra6*).

Mean serum phosphorus concentrations were summarized within categories of covariates. Linear regression was used to estimate associations of individual covariates with differences in mean serum phosphorus concentrations, adjusting for age, sex, race/ethnicity, time of measurement, and fasting status. Additional linear regression models were constructed to estimate the variance in serum phosphorus levels explained by groups of covariates. For these models, continuous covariates were explored using flexible graphing methods and modeled using splines. R^2 values were used to estimate the proportion of variance explained by the model. Locally weighted regression was used to describe the association of dietary phosphorus intake with serum phosphorus concentrations. Error in variables regression was used to examine associations after accounting for variability in dietary phosphorus measurements.

Results

Description of Serum Phosphorus Concentrations in NHANES

Serum phosphorus concentrations were normally distributed with a mean value of 3.4 mg/dL, SD of 0.5 mg/dL, and 25th and 75th percentiles of 3.1 to 3.8 mg/dL (Fig 1). Phosphorus concentrations were greater later in the day and in participants who were not fasting (Fig 2). There was no statistical interaction between time of day and fasting status on serum phosphorus concentration ($P = 0.2$).

Serum phosphorus concentrations did not differ by age in participants aged 30 to 90 years, but were higher in participants aged 20 to 29 years (Fig 3). Phosphorus concentrations were higher in women compared with men (+0.16 mg/dL) and in participants who were Hispanic (+0.06 mg/dL) or non-Hispanic black (+0.07 mg/dL) compared with those who were non-Hispanic white, after adjustment for fasting status and time of day ($P < 0.001$ for each comparison; Table 1; Fig 3). Contrasts by race/ethnicity persisted after adjustment for household income.

The 24-Hour Dietary Recall Data

Greater dietary phosphorus intake was weakly, albeit statistically, associated with higher serum phosphorus concentrations (Table 2; Fig 4). On average, each 500-mg greater intake of dietary phosphorus was associated with a 0.03-mg/dL higher serum phosphorus concentration after adjustment for age, sex, race/ethnicity, time of day, and fasting status ($P < 0.001$). After accounting for observed variability in measured dietary phosphorus intake estimated by using data from the callback sample, each 500-mg greater dietary phosphorus intake was associated with a 0.06-mg/dL higher adjusted serum phosphorus concentration. Associations of each 24-hour dietary intake variable with serum phosphorus concentration were statistically indistinguishable comparing men with women ($P > 0.3$ for each

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

interaction). In a subgroup of participants with an estimated GFR less than 60 mL/min/1.73 m^2, there was no association of dietary phosphorus with serum phosphorus concentration (coefficient, 0.00 mg/dL/500-mg increase; $P = 0.9$; estimated GFR in mL/min/1.73 m^2 may be converted to mL/s/1.73 m^2 by multiplying by 0.01667).

We observed weak correlations of total caloric intake and percentage of calories consumed from carbohydrates with serum phosphorus concentration (Table 2; Fig 4). Percentagess of calories from protein and fat were not associated with serum phosphorus concentration.

The 1-Month Food-Frequency Questionnaire Data

Greater consumption of meat (specifically beef) and dairy products were statistically associated with higher serum phosphorus concentration in participants with estimated GFR of 60 mL/min/1.73 m^2 or greater (Table 3). However, these differences were small (+0.02 or +0.01 mg/dL/serving/d, respectively). Other phosphorus-rich foods were not associated with serum phosphorus concentration in participants with or without chronic kidney disease (Table 3).

Cardiovascular Risk Factors

Associations of serum phosphorus concentrations with individual cardiovascular risk factors were inconsistent and generally modest (Table 4). Serum phosphorus concentrations were slightly higher in participants with hyperlipidemia and those who actively smoked. However, serum phosphorus concentrations were modestly lower in participants with greater body mass index and higher levels of C-reactive protein. No association of serum phosphorus concentration with hypertension or diabetes was observed. In aggregate, higher serum phosphate concentrations were associated with statistically lower 10-year Framingham risk scores for coronary heart disease, primarily because of their association with female sex and younger age. Mean serum phosphorus concentration did not change with estimated GFR until estimated GFR was less than 30 mL/min/1.73 m^2, at which point serum phosphorus concentration markedly increased (+0.66 mg/dL compared with ≥ 90 mL/min/1.73 m^2). We could not detect a statistical association of serum 25-hydroxyvitamin D concentration with serum phosphorus concentration.

Combined Impact of Measured Variables

Time of day and fasting status explained a larger portion of the variance in serum phosphorus concentrations than demographic variables, dietary intakes, or kidney function (Table 5). Combined, time of day, fasting status, demographics, dietary intake, cardiovascular risk factors, and kidney function explained 12% of the variation in serum phosphorus concentrations.

Discussion

Serum phosphorus concentrations were statistically, but only weakly, associated with dietary phosphorus intake and consumption of meat and dairy products in NHANES III, a nationally representative study that emphasized the collection of nutritional data. Serum phosphorus concentrations were not associated with a wide variety of other phosphorus-containing foods and were inversely related to Framingham coronary heart disease risk scores. Altogether, diet, demographics, measurement-related variables, kidney function, and cardiovascular risk factors explained only 12% of the population variation in serum phosphorus concentrations. Thus, factors determining serum phosphorus concentration are largely unknown, and previously observed associations of serum phosphorus concentrations with cardiovascular events are unlikely to reflect differences in dietary intake or traditional cardiovascular risk factors.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Similar dissociations of dietary and serum phosphorus levels recently were observed in a population-based study from Spain and a small group of research volunteers assigned to various phosphorus diets in a controlled setting.[24,25] In the latter study, urinary phosphorus levels were found to increase rapidly in response to dietary phosphorus loading; however, serum phosphorus concentration remained constant.[24] Phosphorus balance is tightly regulated by gastrointestinal absorption, flux into and out of bone, intracellular shift, and renal excretion.[26] Gastrointestinal phosphorus absorption occurs through sodium-phosphorus transporters in the small intestine that are augmented by 1,25-dihydroxyvitamin D.[27] Renal phosphorus excretion is regulated primarily in the proximal tubule by parathyroid hormone and fibroblast growth factor 23 and directly by higher phosphorus concentrations, providing both an immediate and long-term response to phosphorus loading.[28-31]

In patients with moderate CKD, serum phosphorus levels remain within the normal laboratory range because of a significant increase in fractional urinary excretion of phosphorus.[9] Consistent with other studies, we found no association of kidney function with serum phosphorus levels until kidney function was considerably impaired and unlikely to further respond to hormonal stimulation.[7,9] Because severe kidney impairment is uncommon in the general population, it is not surprising that kidney function explained only a very small portion of the variance in serum phosphorus levels in this study.

Of the cardiovascular risk factors studied, only hyperlipidemia and smoking were associated with modestly increased serum phosphorus concentrations, whereas coronary heart disease risk scores were related inversely to serum phosphorus concentrations. These observations support prior conclusions that previous associations of serum phosphorus concentrations with incident cardiovascular events and mortality were unlikely to have been meaningfully confounded by diet, kidney function, or known cardiovascular risk factors.[6,8]

In the absence of diet and traditional cardiovascular risk factors, what are plausible explanations for previous associations of higher serum phosphorus concentrations with incident cardiovascular events and mortality? Given the growing number of hormones recognized to regulate steady-state serum phosphorus levels, it is possible that 1 or more hormones involved in determining the phosphorus set point might contribute to cardiovascular risk through dystrophic mineralization of vascular smooth muscle tissue. However, none of the currently understood regulatory phosphorus hormones have known adverse cardiovascular effects. Given direct effects of higher phosphorus concentrations on smooth muscle calcification in-vitro,[5] it is possible that similar effects may occur in vivo at physiological phosphorus concentrations in the presence of other circulating factors. Phosphorus retention also increases the release of parathyroid hormone and impairs activation of vitamin D[23,32]; high parathyroid hormone and low vitamin D concentrations have each been associated with increased cardiovascular risk in epidemiological studies.[33-35] Finally, it is possible that higher circulating serum phosphorus levels reflect increased bone resorption and osteoporosis, which is associated with vascular calcification.[22] Additional studies are needed to address these important potential mechanisms of association.

We observed variation in nutritional exposure variables over time, which likely reflects both imprecision in dietary recall and true day-to-day differences in dietary practices. Imprecise measurement of exposure variables is expected to bias observed results toward the null association and may partially explain the weak associations observed in this study. Dietary surveys are known to be imprecise; however, the instruments used for NHANES III, which focused on nutritional epidemiology, have been validated and successfully used elsewhere.[13,14] Moreover, the magnitude of association of dietary phosphorus intake with serum

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

phosphorus concentrations remained biologically and clinically small in sensitivity analyses that took into account measured intraindividual variation in reported dietary intake.

We also observed considerable within-individual variation in serum phosphorus concentrations over time. Some of this variation was explained by fasting status and time of day, as previously described,[36] whereas laboratory measurement error, as reported by NHANES III, was relatively small. These findings suggest that a single serum phosphorus measurement does not precisely capture an individual's “average” steady-state phosphorus concentration. Based on normal distribution of the difference in serum phosphorus concentrations from the callback sample, random (nondifferential) measurement error of serum phosphorus concentrations is expected. Unlike random error of nutritional exposure variables, which bias findings toward the null, random error of the outcome variable will decrease statistical power to detect associations by introducing “noise.” The large sample size in the present study mitigates this concern to some extent.

In summary, we found circulating serum phosphorus concentrations to be related weakly to dietary phosphorus intake and unrelated to most phosphorus-containing foods. We could not detect meaningful associations of serum phosphorus concentrations with traditional coronary heart disease risk factors or kidney function within the range of kidney function typically present in the general population. These data suggest that previous prospective associations of higher serum phosphorus concentrations with cardiovascular events are unlikely to be explained by differences in dietary habits or known predisposition to atherosclerosis. Physiological hormones that regulate the serum phosphorus set point require further scrutiny for their possible role in dystrophic calcification and cardiovascular risk.

Acknowledgments

Support: This study was supported by National Institutes of Health Career Development Award K23 DK63274-01 and grant no. 1KL2RR025015-01 from the National Center for Research Resources.

References

1. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphorus product with mortality risk in chronic hemodialysis patients: A national study. Am J Kidney Dis 1998;31:607–617. [PubMed: 9531176]
2. Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: Evidence for the complexity of the association between mineral metabolism and outcomes. J Am Soc Nephrol 2004;15:770–779. [PubMed: 14978180]
3. Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns Study. Kidney Int 2005;67:1179–1187. [PubMed: 15698460]
4. Giachelli CM. Vascular calcification: In vitro evidence for the role of inorganic phosphorus. J Am Soc Nephrol 2003;14(suppl 4):S300–S304. [PubMed: 12939385]
5. Jono S, McKee MD, Murry CE, et al. Phosphorus regulation of vascular smooth muscle cell calcification. Circ Res 2000;87:E10–E17. [PubMed: 11009570]
6. Dhingra R, Sullivan LM, Fox CS, et al. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. Arch Intern Med 2007;167:879–885. [PubMed: 17502528]
7. Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphorus levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 2005;16:520–528. [PubMed: 15615819]
8. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Relation between serum phosphorus level and cardiovascular event rate in people with coronary disease. Circulation 2005;112:2627–2633. [PubMed: 16246962]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

9. Gutierrez O, Isakova T, Rhee E, et al. Fibroblast growth factor-23 mitigates hyperphosphorusmia but accentuates calcitriol deficiency in chronic kidney disease. J Am Soc Nephrol 2005;16:2205–2215. [PubMed: 15917335]
10. Hruska, K.; Slatopolsky, E. Disorders of Phosphorus, calcium, and magnesium metabolism. In: Schrier, R.; Gottschalk, C., editors. Diseases of the Kidney. Vol. 3. London, UK: Little, Brown; 1996. p. 2477-2526.
11. Menon V, Greene T, Pereira AA, et al. Relationship of phosphorus and calcium-phosphorus product with mortality in CKD. Am J Kidney Dis 2005;46:455–463. [PubMed: 16129207]
12. National Center for Health Statistics. Plan and operations of the Third National Health and Nutrition Examination Survey 1988-1994. National Center for Health Statistics. Vital Health Stat 1994;1(32)
13. Hu FB, Rimm E, Smith-Warner SA, et al. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. Am J Clin Nutr 1999;69:243–249. [PubMed: 9989687]
14. Karvetti RL, Knuts LR. Validity of the 24-hour dietary recall. J Am Diet Assoc 1985;85:1437–1442. [PubMed: 4056262]
15. Gunter, E.; Lewis, B.; Koncikowski, S. Laboratory methods used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994 (CD-ROM). Hyattsville, MD: Centers for Disease Control and Prevention; 1996.
16. Genuth S, Alberti KG, Bennett P, et al. Follow-up report on the diagnosis of diabetes mellitus. Diabetes Care 2003;26:3160–3167. [PubMed: 14578255]
17. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–1252. [PubMed: 14656957]
18. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497. [PubMed: 11368702]
19. Coresh J, Astor BC, McQuillan G, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. Am J Kidney Dis 2002;39:920–929. [PubMed: 11979335]
20. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinin. J Am Soc Nephrol 2000;11:0828A. abstr.
21. Mattix HJ, Hsu CY, Shaykevich S, Curhan G. Use of the albumin/creatinine ratio to detect microalbuminuria: Implications of sex and race. J Am Soc Nephrol 2002;13:1034–1039. [PubMed: 11912263]
22. Boukhris R, Becker KL. Calcification of the aorta and osteoporosis. A roentgenographic study. JAMA 1972;219:1307–1311. [PubMed: 5066773]
23. Kates DM, Sherrard DJ, Andress DL. Evidence that serum phosphorus is independently associated with serum PTH in patients with chronic renal failure. Am J Kidney Dis 1997;30:809–813. [PubMed: 9398125]
24. Isakova T, Gutierrez O, Shah A, et al. Postprandial mineral metabolism and secondary hyperparathyroidism in early CKD. J Am Soc Nephrol 2008;19:615–623. [PubMed: 18216315]
25. Mataix J, Aranda P, Lopez-Jurado M, Sanchez C, Planells E, Llopis J. Factors influencing the intake and plasma levels of calcium, phosphorus and magnesium in southern Spain. Eur J Nutr 2006;45:349–354. [PubMed: 16967192]
26. Kestenbaum B. phosphorus metabolism in the setting of chronic kidney disease: Significance and recommendations for treatment. Semin Dial 2007;20:286–294. [PubMed: 17635817]
27. Kaplan RA, Haussler MR, Deftos LJ, Bone H, Pak CY. The role of 1 alpha, 25-dihydroxyvitamin D in the mediation of intestinal hyperabsorption of calcium in primary hyperparathyroidism and absorptive hypercalciuria. J Clin Invest 1977;59:756–760. [PubMed: 192763]
28. Murer H, Hernando N, Forster I, Biber J. Proximal tubular phosphorus reabsorption: Molecular mechanisms. Physiol Rev 2000;80:1373–1409. [PubMed: 11015617]
29. Biber J, Forgo J, Murer H. Modulation of Na+-Pi cotransport in opossum kidney cells by extracellular phosphorus. Am J Physiol 1988;255:C155–C161. [PubMed: 3407761]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

30. Bowe AE, Finnegan R, Jan de Beur SM, et al. FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. Biochem Biophys Res Commun 2001;284:977–981. [PubMed: 11409890]

31. Kempson SA, Lotscher M, Kaissling B, Biber J, Murer H, Levi M. Parathyroid hormone action on phosphate transporter mRNA and protein in rat renal proximal tubules. Am J Physiol 1995;268:F784–F791. [PubMed: 7733336]

32. Yoshida T, Yoshida N, Monkawa T, Hayashi M, Saruta T. Dietary phosphorus deprivation induces 25-hydroxyvitamin D(3) 1alpha-hydroxylase gene expression. Endocrinology 2001;142:1720–1726. [PubMed: 11316734]

33. Hedback G, Oden A. Increased risk of death from primary hyperparathyroidism—An update. Eur J Clin Invest 1998;28:271–276. [PubMed: 9615902]

34. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503–511. [PubMed: 18180395]

35. Watson K. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation 1997;96:1755–1760. [PubMed: 9323058]

36. Portale AA, Halloran BP, Morris RC Jr. Dietary intake of phosphorus modulates the circadian rhythm in serum concentration of phosphorus. Implications for the renal production of 1,25-dihydroxyvitamin D. J Clin Invest 1987;80:1147–1154. [PubMed: 3654974]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

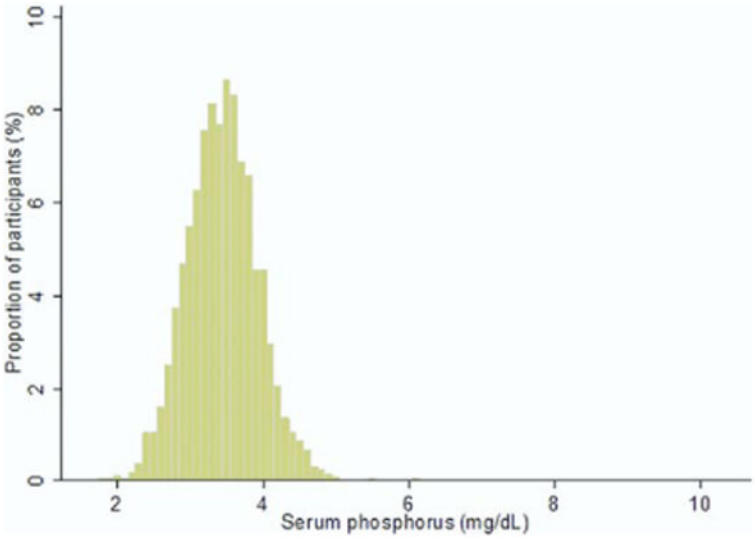

Figure 1.
Distribution of serum phosphorus concentrations in the Third National Health and Nutrition Examination Survey. Serum phosphorus in mg/dL may be converted to mmol/L by multiplying by 0.3229.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

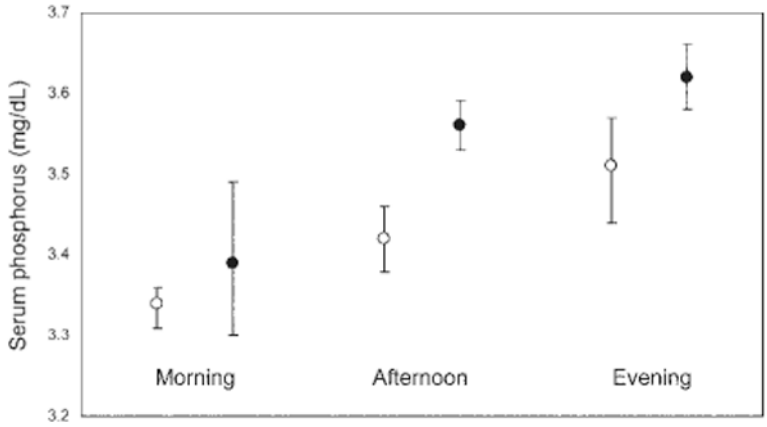

Figure 2.

Mean serum phosphorus concentrations by time of day and fasting status. Open circles, fasting; filled circles, nonfasting; bars, 95% confidence intervals. Serum phosphorus in mg/dL may be converted to mmol/L by multiplying by 0.3229.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

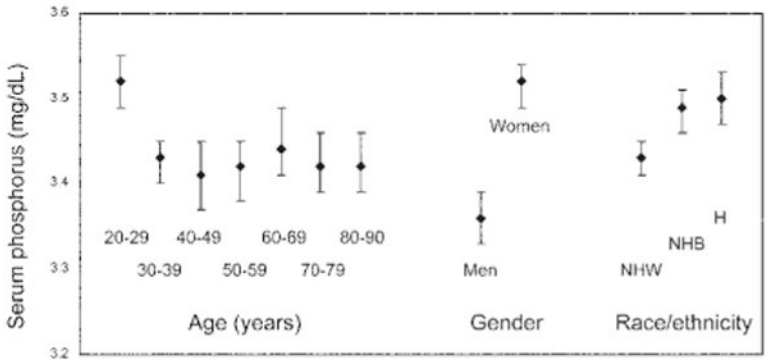

Figure 3.

Mean serum phosphorus concentrations by age, sex, and race/ethnicity. Bars represent 95% confidence intervals. Abbreviations: NHW, non-Hispanic white; NHB, non-Hispanic black; H, Hispanic. Serum phosphorus in mg/dL may be converted to mmol/L by multiplying by 0.3229.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

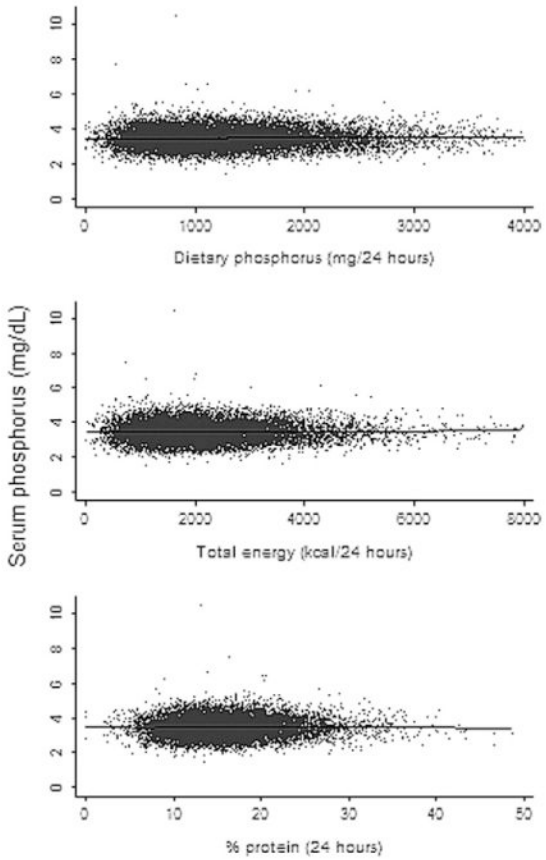

Figure 4.

Relationship of serum phosphorus concentration to 24-hour dietary phosphorus, total energy, and percentage of protein intake. Serum phosphorus in mg/dL may be converted to mmol/L by multiplying by 0.3229.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1
Demographics by Serum Phosphorus Concentration

	<3.0 mg/dL	3.0-3.4 mg/dL	3.5-3.9 mg/dL	≥4.0 mg/dL
Weighted percent	15 (2,499)	35 (5,738)	35 (6,324)	14 (4,162)
Mean age (y)	46.9 ± 0.5	45.3 ± 0.6	43.7 ± 0.6	44.2 ± 0.7
Women (%)	37	49	58	62
Race (%)				
White	79	78	75	74
Black	10	9	11	12
Mexican	4	5	5	6
Diabetes mellitus (%)	6	5	5	7
Hypertension (%)	28	25	22	24
Chronic kidney disease	7 (259)	7 (557)	7 (536)	10 (303)

Note: Values expressed as percent (no.) or mean ± SD, unless otherwise indicated. Serum phosphorus in mg/dL may be converted to mmol/L by multiplying by 0.3229.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 2
Associations of 24-Hour Dietary Recall Variables With Serum Phosphorus Concentration

		Serum Phosphorus Concentration (mg/dL)		
24-Hour Dietary Recall Variable	**No. of Patients**	**Unadjusted Mean (95% confidence interval)**	**Adjusted Difference* (95% confidence interval)**	***P***
Energy (kcal)				0.2
<1,500	4,748	3.47 (3.44 to 3.49)	−0.01 (−0.04 to 0.02)	
1,500-2,300	5,347	3.45 (3.42 to 3.47)	Reference	
>2,300	4,890	3.42 (3.39 to 3.45)	0.02 (−0.01 to 0.06)	
500-kcal increase			0.01 (0.00 to 0.02)	0.005
Protein (% energy)				0.4
<13	4,472	3.44 (3.41 to 3.46)	−0.01 (−0.03 to 0.02)	
13-17	5,478	3.44 (3.41 to 3.46)	Reference	
>17	5,035	3.45 (3.43 to 3.48)	0.01 (−0.01 to 0.04)	
10% increase			0.02 (0.00 to 0.04)	0.07
Carbohydrate (% energy)				0.07
<45	4,906	3.44 (3.41 to 3.47)	0.02 (−0.01 to 0.04)	
45-55	5,328	3.44 (3.42 to 3.47)	Reference	
>55	4,751	3.44 (3.42 to 3.47)	−0.01 (−0.04 to 0.02)	
10% increase			−0.01 (−0.02 to 0.00)	0.02
Total fat (% energy)				0.3
<30	5,262	3.44 (3.41 to 3.46)	−0.02 (−0.05 to 0.01)	
30-38	5,025	3.44 (3.42 to 3.47)	Reference	
>38	4,698	3.44 (3.42 to 3.47)	0 (−0.02 to 0.02)	
10% increase			0.01 (−0.01 to 0.02)	0.4
Phosphorus (mg)				<0.001
<900	5,063	3.44 (3.41 to 3.46)	−0.02 (−0.05 to 0.01)	
900-1,400	5,052	3.44 (3.41 to 3.46)	Reference	
>1,400	4,870	3.45 (3.42 to 3.48)	0.07 (0.04 to 0.1)	
500-mg increase			0.03 (0.02 to 0.04)	<0.001

*Adjusted for age, sex, race/ethnicity, time of day, and fasting status.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

Table 3
Associations of Selected Food-Frequency Questionnaire Items With Serum Phosphorus Concentration

	No Chronic Kidney Disease			Chronic Kidney Disease		
Food Item (average daily servings)	**Coefficient**	**95% Confidence Interval**	***P***	**Coefficient**	**95% Confidence Interval**	***P***
Meat (1.1)	0.02	0.01 to 0.04	0.01	−0.01	−0.06 to 0.03	0.6
Seafood (0.1)	−0.04	−0.11 to −0.03	0.3	0.06	−0.11 to 0.24	0.5
Dairy (1.7)	0.01	0.00 to 0.02	0.02	−0.01	−0.05 to 0.02	0.5
Bacon/sausage (0.3)	0.02	−0.01 to 0.05	0.1	0.01	−0.01 to 0.03	0.2
Organs (0.0)	−0.01	−0.16 to 0.14	0.9	0.04	−0.85 to 0.93	0.9
Beef (0.4)	0.04	0.00 to 0.08	0.04	−0.15	−0.29 to −0.01	0.04
Pork/ham (0.1)	0.04	−0.02 to 0.11	0.2	−0.08	−0.28 to 0.12	0.4
Chicken/turkey (0.3)	0.01	−0.04 to 0.07	0.6	−0.07	−0.21 to 0.07	0.3
Shrimp/shellfish (0.1)	−0.11	−0.23 to 0.01	0.08	−0.03	−0.43 to 0.37	0.9
Fish (0.2)	−0.03	−0.12 to 0.06	0.6	0.10	−0.11 to 0.31	0.4
Chocolate milk/hot cocoa (0.1)	0.05	0.00 to 0.10	0.06	−0.07	−0.20 to 0.07	0.3
Milk (0.8)	0.01	0.00 to 0.03	0.07	−0.01	−0.06 to 0.03	0.5
Yogurt/frozen yogurt (0.1)	−0.01	−0.08 to 0.07	0.9	0.00	−0.13 to 0.12	0.9
Ice cream/milkshakes (0.2)	0.01	−0.03 to 0.06	0.5	−0.04	−0.13 to 0.04	0.3
Cheese (0.4)	0.02	−0.01 to 0.06	0.1	0.01	−0.07 to 0.09	0.8
Pizza/lasagna (0.1)	−0.02	−0.11 to 0.07	0.7	−0.04	−0.69 to 0.60	0.9
Cheese dishes (0.1)	−0.01	−0.08 to 0.07	0.9	−0.01	−0.41 to 0.38	0.9

Am J Kidney Dis. Author manuscript; available in PMC 2011 February 28.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 4
Associations of Cardiovascular Risk Factors With Serum Phosphorus Concentration

Covariate	No. of Patients	Serum Phosphorus Concentration (mg/dL)		*P*
		Unadjusted Mean (95% confidence interval)	Adjusted Difference* (95% confidence interval)	
Diabetes mellitus				0.2
No	14,215	3.44 (3.42 to 3.46)	Reference	
Yes	1,280	3.48 (3.43 to 3.53)	0.03 (−0.02 to 0.07)	
Hypertension				0.2
No	10,717	3.45 (3.43 to 3.48)	Reference	
Yes	4,771	3.41 (3.39 to 3.44)	−0.02 (−0.05 to 0.01)	
Hyperlipidemia				<0.001
No	12,026	3.43 (3.41 to 3.46)	Reference	
Yes	3,450	3.48 (3.45 to 3.5)	0.06 (0.03 to 0.08)	
Smoking				0.001
Never	7,654	3.45 (3.42 to 3.48)	Reference	
Former	3,863	3.39 (3.36 to 3.42)	0 (−0.03 to 0.03)	
Current	3,996	3.48 (3.45 to 3.51)	0.06 (0.03 to 0.09)	
Body mass index (kg/m^2)				<0.001
<18.5	308	3.58 (3.51 to 3.65)	0.07 (0.01 to 0.13)	
18.5-24.9	5,913	3.47 (3.44 to 3.49)	Reference	
25-29.9	5,395	3.42 (3.39 to 3.45)	−0.02 (−0.04 to 0.01)	
30-34.9	2,477	3.41 (3.38 to 3.44)	−0.05 (−0.08 to −0.01)	
≥35	1,385	3.43 (3.39 to 3.47)	−0.05 (−0.09 to −0.01)	
Serum C-reactive protein (mg/dL)				0.03
<0.21	10,141	3.45 (3.42 to 3.47)	Reference	
≥0.21	5,360	3.44 (3.41 to 3.47)	−0.03 (−0.05 to 0)	
10-y Framingham risk score				<0.001
<10%	7,338	3.49 (3.46 to 3.51)	Reference	
10%-20%	1,459	3.38 (3.34 to 3.42)	−0.10 (−0.15 to −0.06)	
>20%	441	3.33 (3.27 to 3.40)	−0.15 (−0.22 to −0.08)	
Estimated glomerular filtration rate† (mL/min/1.73 m^2)				<0.001
<30	69	4.09 (3.82 to 4.36)	0.66 (0.4 to 0.91)	
30-44.9	298	3.46 (3.4 to 3.52)	0.03 (−0.04 to 0.09)	
45-59.9	1,134	3.48 (3.44 to 3.52)	0.05 (0 to 0.1)	
60-89.9	7,624	3.43 (3.41 to 3.45)	0 (−0.04 to 0.03)	
≥90	6,387	3.45 (3.42 to 3.48)	Reference	
Urine albumin-creatinine ratio‡				0.05
Normal	12,744	3.45 (3.42 to 3.47)	Reference	
Microalbuminuria	2,067	3.41 (3.38 to 3.44)	−0.04 (−0.07 to −0.01)	
Macroalbuminuria	322	3.43 (3.34 to 3.52)	−0.02 (−0.12 to 0.08)	

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Note: Glomerular filtration rate in mL/min/1.73 m^2 may be converted to mL/s/1.73 m^2 by multiplying by 0.01667.

[*] Adjusted for age, sex, race/ethnicity, time of day, and fasting status (10-year Framingham risk score adjusted race/ethnicity, time of day, and fasting status only).

[†] Calculated using the simplified Modification of Diet in Renal Disease Study equation.[20]

[‡] Urine albumin-creatinine ratio defined as normal (<17 mg/g for men, <25 mg/g for women), microalbuminuria (17 to 249 mg/g for men, 25 to 354 mg/g for women), or macroalbuminuria (≥250 mg/g for men, ≥355 mg/g for women).[21]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Table 5

Variation in Serum Phosphorus Concentrations Explained by Groups of Potential Determinants

Potential Determinants	Univariate R^2	Cumulative R^2
Fasting status, time of day	0.05	
Age, sex, race/ethnicity	0.04	0.09
Dietary variables*	0.01	0.11
Estimated glomerular filtration rate	0.007	0.11
Cardiovascular risk factors†	0.01	0.12

*Dietary variables include total energy, protein, carbohydrate, total fat, phosphorus, alcohol, dairy, meat, and seafood.

†Cardiovascular risk factors include diabetes, hypertension, hypercholesterolemia, smoking, body mass index category, C-reactive protein level greater than 0.21 mg/dL, and albuminuria.