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Relation of Serum Phosphorus Levels to Ankle Brachial Pressure Index (From the Third National Health and Nutrition Examination Survey)

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Abstract

Higher levels of serum phosphorus that remain within the reference range are associated with increased risk of cardiovascular disease (CVD). However, the mechanisms by which higher serum phosphorus concentrations may contribute to the development of CVD remain unclear. Cross-sectional association between serum phosphorus levels and arterial stiffness as estimated by an ankle brachial pressure index (ABPI) >1.3, was examined in 581 participants in the Third National Health and Nutrition Examination Survey. Logistic regression analysis was performed to evaluate whether higher serum phosphorus levels were associated with high ABPI, independently of several potential confounders. Among the 581 participants, 38% and 10% had a serum phosphorus levels >3.5 and >4.0 mg/dL, respectively. An ABPI >1.3 was present in 7.3% of participants. Higher quartiles of serum phosphorus levels were associated with a greater prevalence of high ABPI: 5.4%, 3.7%, 7.8%, and 12.9% for quartiles 1 (<3.1 mg/dL), 2 (3.1 to 3.4 mg/dL), 3 (3.4 to 3.7 mg/dL) and 4 (3.7 to 5.0 mg/dL), respectively. There was a strong, positive association between the highest quartile of serum phosphorus (3.7 to 5.0 mg/dL) and high ABPI when compared to the reference group (3.1 to 3.4 mg/dL) after adjustment for demographics, traditional CVD risk factors, kidney function, C-reactive protein, serum calcium, and 25-hydroxyvitamin D levels (adjusted odds ratio 4.78, 95% CI 1.73 to 13.2; p=0.003). In conclusion, serum phosphorus levels, even within the reference range, are independently associated with high ABPI, a marker of arterial stiffness, in the US adult population.

Keywords

Serum phosphorus; arterial stiffness and ankle brachial pressure index

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INTRODUCTION

The ankle brachial pressure index (ABPI) is a non-invasive tool used to evaluate vascular stiffness and is a strong predictor of cardiovascular disease (CVD) morbidity and mortality [1]. Non compressible calcified arteries result in abnormally high ABPI values (i.e., ABPI >1.3), whereas peripheral arterial disease (PAD) is defined as an ABPI < 0.9 [1,2]. The relation between serum phosphorus concentrations and PAD has been evaluated [3], but the association between serum phosphorus and vascular stiffness (as estimated by ABPI >1.3) has not been thoroughly examined in the US general population. The purpose of the present analysis is to investigate the relationship between serum phosphorus levels concentrations and ABPI >1.3 in US adults. We tested the hypothesis that higher serum phosphorus levels are associated with high ABPI values in the general US adult population.

METHODS

The Third National Health and Nutrition Examination Survey (NHANES III) is a national probability survey of Americans conducted between 1988 and 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention [4]. The survey was designed to obtain information on health and nutritional status of the non-institutionalized US population. A stratified, multistage sampling design was used, with over-sampling of Non-Hispanic blacks, Mexican-Americans, and persons over the age of 60 years. Standardized questionnaires were administered in the home, followed by a detailed physical examination and blood specimens at a mobile examination center.

This analysis was restricted to the 581 participants of 40 years or older who had complete data for serum phosphorus, ABPI measurements and calculation of estimated glomerular filtration rate (eGFR) by the abbreviated Modification of Diet in Renal Disease formula (MDRD) [5].

Serum phosphorus level was the main predictor for all analyses. Serum phosphorus levels concentrations were measured using a Hitachi 737 automated analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN) with a reportable range of 0.5–20 mg/dL, and a coefficient of variation between 0.52% and 2.43% for pooled controls [4]. For this analysis, serum phosphorus levels were divided into quartiles: quartile 1: < 3.1, quartile 2: 3.1–3.4, quartile 3: 3.4–3.7, and quartile 4: 3.7–5.0 mg/dL, respectively. A serum phosphorus level of 3.1–3.4 mg/dL was chosen as the reference range based on previous data showing a higher risk of CVD with phosphorus levels >3.5 mg/dL [6,7,8].

The primary outcome of interest was peripheral arterial stiffness as estimated by ABPI. Systolic blood pressure was measured in the supine position in the right arm (brachial artery) and in the posterior tibial artery of both ankles with an 8-MHZ Doppler. Each pressure was measured twice in participants aged 40–59 and once in participants aged >60 to reduce the time for this component in that age group. All blood pressure measurements were performed in a standardized fashion at the mobile examination centers [4]. The ABPI was calculated by dividing the mean systolic blood pressure in the ankle by the mean systolic blood pressure in the arm. The normal range for ABPI is from 1.0 to 1.3. A high ABPI was defined as >1.3 in either leg based on prior studies showing an ABPI >1.3 is a reliable marker of peripheral vascular stiffness [9]. Data on incompressible arteries was not available.

Questionnaire data included self-reported age, gender and race/ethnicity. Race/ethnicity was divided into four categories: non-Hispanic white, non-Hispanic black, Mexican-American

and other. Participants were defined as having hypertension if they were taking antihypertensive medications, reported being told by a physician that they have high blood pressure, or the average of three blood pressure readings was a systolic blood pressure of 140 mmHg or higher, or a diastolic blood pressure of 90 mmHg or higher. Diabetes was diagnosed if participants were taking medication for diabetes, or had a fasting plasma glucose concentration of 126 g/dL or higher or when a physician had ever told them that they had diabetes mellitus. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Smoking status was classified as never, former, or current smoker. Glomerular filtration rate was estimated from the abbreviated MDRD Study equation [5] as follows: $eGFR = 186.3 \times (\text{serum creatinine mg/dl})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$. Serum creatinine measurements (measured on a Hitachi 704 Analyzer by using a kinetic rate Jaffé method) were recalibrated to the Cleveland Clinic “standard” assay used in the development of the MDRD GFR prediction equation to ensure validity of the results. Serum concentrations of 25 hydroxyvitamin D [25(OH)D] were measured using an INCSTAR 25(OH)D two step assay procedure with a coefficient of variation <10%. C-reactive protein (CRP) was measured by latex-enhanced nephelometry (Behring Diagnostics, Inc., Somerville, NJ) with the lower limit of detection of 0.21 mg/dL, and pooled controls had a coefficient of variation between 3.3% and 16.1%. Fasting levels of total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were measured by a Hitachi 704 Analyzer. Low-density lipoprotein (LDL-C) cholesterol concentration was calculated using the Friedewald equation [10].

Univariate modeling was first performed to determine if a relationship existed between variables and quartiles of serum phosphorus. Categorical variables were examined with a Cochran-Armitage trend test and continuous variables were examined with one-way analysis of variance (ANOVA). Observations were weighted to reflect the general US population as of early 1990s, using weights calculated for that purpose by the National Health Statistics [11]. The independent effect of serum phosphorus levels on high ABPI (defined as $ABPI > 1.3$) was studied using logistic regression models, adjusting simultaneously for several covariates. We chose covariates as candidate confounding factors based on their biological plausibility or based on prior studies. The following covariates were included: age, sex, race/ethnicity, BMI, smoking status, hypertension, diabetes, eGFR, LDL-C, HDL-C, CRP, calcium and 25(OH)D. In our analysis, serum phosphorus was evaluated as both an ordinal (quartiles of serum phosphorus) and as a continuous variable. Of note, we examined age, BMI, eGFR, LDL-C and HDL-C as both continuous and categorical variables, but present results using the categorical treatment, as results were similar. Analyses were conducted using SAS software, version 9.1.3. P values <0.05 were considered statistically significant.

RESULTS

Among the 581 participants, 38% and 10% had a serum phosphorus level >3.5 and >4.0 mg/dL, respectively; only 1.5 % of them had a serum phosphorus concentration above the normal laboratory range of 4.5 mg/dL. Baseline characteristics of the entire population stratified according to quartiles of serum phosphorus levels are shown in Table 1.

Association of ABPI and Serum Phosphorus Levels

An $ABPI > 1.3$ was present in 7.3% of the study population. There were no significant differences in age, sex, race, BMI, smoking status, diabetes, hypertension, eGFR, 25(OH)D, calcium, CRP, LDL-C or HDL-C levels between participants with higher vs. lower ABPI (data not shown). The mean ($\pm$ SD) serum phosphorus levels were significantly higher in subjects with $ABPI > 1.3$ than in those with an $ABPI \leq 1.3$ (3.6 ± 0.6 mg/dL vs. 3.4 ± 0.5 mg/dL, respectively; $p=0.009$).

As shown in Figure 1, higher quartiles of serum phosphorus levels were associated with higher prevalence of ABPI >1.3: 5.4%, 3.7%, 7.8%, and 12.9% for quartile 1 (<3.1 mg/dL), quartile 2 (3.1–3.4 mg/dL), quartile 3 (3.4–3.7 mg/dL) and quartile 4 (3.7–5.0 mg/dL), respectively. ($p=0.005$ for trend).

Figure 2 shows the association between higher serum phosphorus levels and high ABPI. Serum phosphorus levels in the highest quartile (3.7 to 5.0 mg/dL) were a strong correlate of high ABPI when compared to the reference phosphorus group (3.1 to 3.4 mg/dL) in both unadjusted and fully adjusted logistic regression models. After adjustment for age, sex, race/ethnicity, BMI, smoking status, hypertension, diabetes, eGFR, LDL-C, HDL-C, CRP, calcium and 25(OH)D levels, the highest quartile of serum phosphorus was associated with approximately 5-fold increased risk of high ABPI (adjusted OR 4.78, 95% Confidence Interval (CI) 1.73 to 13.2; $p=0.003$). Serum phosphorus levels in the third quartile (3.4–3.7 mg/dL) tended toward an increased risk of high ABPI compared to the reference group, but did not reach statistical significance (adjusted OR 2.55, 95% CI 0.85 to 7.68; $p=0.09$); serum phosphorus levels in the lowest quartile (< 3.1 mg/dL) were not significantly associated with high ABPI. When serum phosphorus levels was evaluated as a continuous variable in the fully adjusted regression model, the association between higher serum phosphorus levels and high ABPI remained highly significant (adjusted OR 2.97, 95% CI 1.47 to 6.01, per 1 mg/dL increase in serum phosphorus levels; $p=0.003$). Results did not change when the primary predictor was replaced by sex-specific quartiles of serum phosphorus. Furthermore, all above-mentioned significant results did not change when participants with an ABPI < 0.9 were excluded from the analysis.

DISCUSSION

The major finding of this study is that higher serum phosphorus levels, even within the normal laboratory range, are independently associated with a ABPI >1.3, a reliable marker of arterial stiffness, in the US adult population. The risk of high ABPI increased across quartiles of serum phosphorus levels. Furthermore, subjects in the highest quartile of serum phosphorus (3.7–5.0 mg/dL) had a 5-fold greater odds of high ABPI than those with serum phosphorus levels in the reference range (3.1–3.4 mg/dL) after adjustment for a broad spectrum of traditional and non-traditional CVD risk factors, including kidney function, CRP, LDL-C, HDL-C and 25(OH)D levels. Hence, given the availability and low cost of serum phosphorus assays our findings may prove clinically useful those patients at higher risk for vascular stiffness.

A high ABPI >1.3 suggests calcification of the medial arterial wall and incompressible vessels reflecting arterial stiffness, which has been associated with increased risk of cardiovascular morbidity and mortality [9,12]. In American Indians with and without kidney disease, an ABPI >1.4 is independently associated with all-cause and cardiovascular mortality (hazard ratio [HR] 1.77, 95% CI 1.48 to 2.13 and HR 2.09, 95% CI 1.49 to 2.94, respectively)[13]. In addition, among generally healthy, community-dwelling older adults, aortic pulse wave velocity, a marker of arterial stiffness, is associated with higher cardiovascular mortality, coronary heart disease, and stroke [14]. Similarly, in chronic hemodialysis patients, an ABPI >1.3 is associated with a 2-fold increased risk of all-cause mortality and a 3-fold increased risk of cardiovascular mortality (HR 2.77, 95% CI 1.11 to 4.89 and HR 3.04, 95% CI 1.14 to 8.12, respectively) [15].

Overall, our findings are hypothesis generating and suggest that the previously observed association of higher serum phosphorus concentrations with the future risk of CVD events [6–8,16,17] might be, at least in part, mediated by increased peripheral arterial stiffness. This hypothesis is also indirectly supported by recent experimental data showing that high

dietary phosphorus load acutely impairs endothelial function, assessed as brachial flow-mediated vasodilation, in healthy men [18]. Our findings are corroborated by the recent results from the Multi-Ethnic Study of Atherosclerosis (MESA) showing a significant association between higher serum phosphorus levels and high ABPI among individuals with normal kidney function to moderate kidney disease and no clinical evidence of CVD [19]. Moreover, in accord with other large observational studies [20,21], we confirmed that subjects with higher serum phosphorus concentrations have a more favorable profile of traditional CVD risk factors than those with lower serum phosphorus concentrations, suggesting that the previously observed associations of serum phosphorus concentrations with incident CVD events are unlikely to be a result of differences in traditional CVD risk factors. Notably, we found that subjects with higher serum phosphorus concentrations have a less favorable profile of some non-traditional CVD risk factors – i.e., higher serum CRP levels and lower serum 25(OH)D levels – that might partially contribute to the increased peripheral arterial stiffness as well as to the relationship between serum phosphorus levels and the risk for incident CVD events.

Our study has several limitations and strengths that should be considered. First, the cross-sectional design precludes evaluation of temporality, or to evaluate what influence changes in serum phosphorus levels over time may have on high ABPI. Second, we could not evaluate any possible effects of serum parathyroid hormone levels because measurements of this variable were not performed in NHANES III. Yet prior studies in community-living populations show associations of hyperparathyroidism with CVD events [22], and higher parathyroid hormone should be associated with lower serum phosphorus levels, thus we believe it is unlikely that differences in parathyroid hormone confound results demonstrated here. Third, arm blood pressure was only available in one arm, data on incompressible leg arteries were not available, and older individuals only had leg blood pressure recorded once rather than twice. These measurement issues may have resulted in some misclassification between normal and high ABPI groups that would likely have biased the results towards the null hypothesis.

Notwithstanding these limitations, our study also has several important strengths. First, it is a comprehensive national survey to estimate the association between serum phosphorus and high ABPI in the US adult population. Second, NHANES III used uniform methods to collect data on ABPI, phosphorus, calcium, 25(OH)D, CRP and all other laboratory measurements. Third, the available data on other important risk factors associated with arterial stiffness and medial calcification allowed us to give an unbiased estimate for the relationship between serum phosphorus and ABPI.

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Figure 1.
Prevalence of High Ankle Brachial Pressure Index (defined as ABPI > 1.3) According to Quartiles of Serum Phosphorus Levels

Figure 2.

Odds Ratios of High Ankle Brachial Pressure Index (defined as ABPI >1.3) According to Quartiles of Serum Phosphorus Levels. Fully adjusted models were adjusted for age, gender, race/ethnicity, body mass index, smoking status, hypertension, diabetes, estimated glomerular filtration rate, low-density lipoprotein cholesterol, high density lipoprotein cholesterol, C-reactive protein, calcium and 25-hydroxuvitamin D.

Table 1
 Characteristics of 581 Participants according to Quartiles of Serum Phosphorous Levels

Characteristics	Serum Phosphorus Level (mg/dL)				P-value for trend
	< 3.1 (N=143)	3.1 – 3.4 (N=159)	3.4 – 3.7 (N=125)	3.7 – 5.0 (N=154)	
Age (years)	56 ± 14	58 ± 13	57 ± 14	59 ± 12	0.38
Male	62.0%	49.0%	43.0%	32.0%	
Female	38.0%	51.0%	57.0%	68.0%	<0.0001
Non-Hispanic white	84.0%	81.0%	80.0%	77.0%	
Non-Hispanic black	7.0%	10.0%	10.0%	9.0%	
Mexican American	2.5%	3.0%	4.0%	5.0%	0.84
Other	6.5%	6.0%	6.0%	9.0%	
BMI (kg/m ²)					
< 25	43.0%	37.0%	46.0%	39.0%	
25–29	33.0%	40.0%	28.0%	33.0%	0.41
≥ 30	24.0%	23.0%	26.0%	28.0%	
Smoking					
Never	40.0%	34.0%	32.0%	50.0%	
Former	31.0%	39.0%	40.0%	34.0%	0.02
Current	29.0%	27.0%	28.0%	16.0%	
Diabetes mellitus	9.5%	8.6%	8.9%	12.3%	0.41
Hypertension	29.0%	37.0%	33.0%	36.0%	0.35
Estimated GFR (mL/min/1.73m ²)					
≥ 90	40.0%	54.0%	47.0%	44.0%	
60–89	50.0%	42.0%	46.0%	51.0%	
<60	10.0%	4.0%	7.0%	5.0%	0.13
25-hydroxyvitamin D (ng/mL)	29.0 ± 10.5	24.8 ± 8.9	27.4 ± 9.4	27.6 ± 9.6	0.001
Calcium (mg/dL)	9.2 ± 0.4	9.3 ± 0.5	9.3 ± 0.4	9.3 ± 0.5	0.02
Phosphorus (mg/dL)	2.8 ± 0.2	3.3 ± 0.9	3.6 ± 0.1	4.1 ± 0.3	ND

Characteristics	Serum Phosphorus Level (mg/dL)				P-value for trend
	< 3.1 (N=143)	3.1 –3.4 (N=159)	3.4 – 3.7 (N=125)	3.7 – 5.0 (N=154)	
CRP (mg/dL)	0.38 ± 0.6	0.46 ± 0.7	0.38 ± 0.4	0.58 ± 0.8	0.03
LDL-C (mg/dL)	129 ± 44	134 ± 41	135 ± 35	137 ± 35	0.34
HDL-C (mg/dL)	48 ± 16	51 ± 16	57 ± 24	54 ± 15	0.0003

BMI=body mass index; kg=kilograms; m=meters; GFR=glomerular filtration rate; CRP=Creative protein; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol