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Relation of Serum Phosphorus Levels to Carotid Intima-media Thickness in Asymptomatic Young Adults (from the Bogalusa Heart Study)

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Abstract

Elevated serum phosphorus has been associated with increased mortality from cardiovascular (CV) disease. However, information is scant regarding the influence of serum phosphorus within the normal range on vascular risk in terms of subclinical atherosclerosis in asymptomatic young adults. Serum phosphorus along with other CV risk factor variables were measured in 856 white and 354 black subjects without known CV disease or renal disease. Carotid intima-media thickness (IMT) was measured by B-mode ultrasonography. Significant race and sex differences were noted for serum phosphorus (blacks>whites) and carotid IMT (black females>white females; males>females). In bivariate analyses, serum phosphorus was correlated with carotid IMT ($p<0.001$); and smokers showed higher phosphorus levels than nonsmokers ($p=0.008$). In multivariate regression analyses, carotid IMT was significantly associated with serum phosphorus (regression coefficient $\beta=0.028$, $p<0.001$) and smoking ($\beta=0.032$, $p<0.001$), adjusting for other CV risk factors and estimated glomerular filtration rate. In addition, a significant interaction effect of cigarette smoking and serum phosphorus on carotid IMT was noted, with a greater increasing trend of carotid IMT with phosphorus in smokers than that in nonsmokers ($p=0.019$ for interaction). In conclusion, serum phosphorus within the normal range is an important correlate of carotid IMT in asymptomatic young adults, with smoking potentiating this adverse association.

Keywords

phosphorus; carotid artery; carotid intima-media thickness; cigarette smoking; atherosclerosis

Phosphorus is essential for diverse biological functions and is tightly regulated within the physiological range in healthy subjects.^{1,2} Excess amount of phosphorus has been associated with increased mortality from cardiovascular (CV) disease in subjects with chronic kidney disease, ranging from moderate to end stage renal failure.^{3–7} Recently, it has been found that phosphorus levels within a normal range are independently associated with the risk of all-cause mortality and CV events in people with previous myocardial infarction.⁸

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Phosphorus levels are also associated with increased risk of chronic kidney disease,⁹ and may be a potentially modifiable risk factor for stroke and death in a general population.¹⁰ However, only a few studies have examined the relationship between phosphorus levels and subclinical atherosclerosis in asymptomatic individuals.^{11,12} The present study examines the relationship between serum phosphorus and carotid intima-media thickness (IMT), a validated indicator of subclinical atherosclerosis and future CV risk,^{13–15} in clinically asymptomatic white and black young adults.

Materials and Methods

As part of the Bogalusa Heart Study, a biracial (black-white) community-based investigation of the early nature history of CV disease, A total of 1210 subjects (856 whites and 354 blacks; 43.1% males) aged 24–44 years, residing in the community of Bogalusa, LA, were examined for carotid IMT by ultrasound and CV risk factor variables, including serum phosphorus. All subjects in this study gave informed consent for examination. Study protocols were approved by the Institutional Review Board of the Tulane University Medical Center.

Examinations of study subjects followed the protocols and procedures described elsewhere.¹⁶ Subjects were instructed to fast for 12 hours before screening, and the compliance was determined by an interview on the morning of examination. Height and weight were measured twice to ± 0.1 cm and to ± 0.1 kg, respectively. Body mass index (BMI=weight in kilograms divided by the square of the height in meters) was used as a measure of overall adiposity. Blood pressure levels were measured using mercury sphygmomanometers on the right arm of subjects in a relaxed, sitting position by two randomly assigned nurses (three replicates each). The first and fifth Korotkoff phases were used to determine systolic and diastolic blood pressure, respectively. Means of replicate readings were used for analyses. Forced values (140/90mmHg) were assigned for systolic and diastolic blood pressure, respectively, to subjects (n=81) who were on anti-hypertension medication at the time of examination. Mean arterial pressure (MAP=diastolic blood pressure + 1/3 pulse pressure) was used as a measure of hemodynamic status. Information on smoking status was obtained by questionnaires. Those who smoked at least one cigarette per week during the past one year were considered as current smokers.

Serum phosphorus levels were determined by the ammonium molybdate method, glucose and creatinine by an enzymatic method, as part of multiple chemistry profile (SMA20) by the multichannel Olympus Au-5000 Analyzer (Olympus, Lake Success, NY). Serum cholesterol and triglycerides (TG) were determined enzymatically¹⁷ on the Hitachi 902 Automatic Analyzer (Roche Diagnostics, Indianapolis, IN). Serum lipoprotein cholesterol were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures.¹⁸ The laboratory is being monitored for precision and accuracy by the Lipid Standardization Program of the Centers for Disease Control and Prevention, Atlanta, GA. Plasma insulin was measured by a commercial radioimmunoassay kit (Padebas insulin kits, Pharmacia, Diagnostics, Piscataway, NJ); Intra-class correlation coefficients, a measure of reproducibility of the entire process from blood collection to data processing, between the blind duplicate values (n=97) were 0.98 for low-density lipoprotein cholesterol (LDL-C), 0.99 for high-density lipoprotein cholesterol (HDL-C), 0.97 for TG, 0.98 for both glucose and insulin, 0.98 for creatinine and 0.99 for serum phosphorus. Glomerular filtration rate (eGFR) was estimated as a function of age, serum creatinine, gender and race using the simplified Modified Diet in Renal Disease (MDRD) equation¹⁹: $eGFR \text{ (mL/min/1.73m}^2\text{)} = 186.3 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$, where m^2 denotes body surface area in squared meter. An index of insulin resistance (homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the formula:²⁰

fasting insulin $\mu\text{U/mL} \times \text{fasting glucose (mmol/L)}/22.5$. Forced values of 160mg/dL for LDL-C and 126 mg/dL for glucose were assigned to subjects who were on medications for hypercholesterolemia (n=26) and diabetes (n=19) at the time of examination, respectively.

Carotid ultrasound measurements were done by an experienced and highly trained technician on a Toshiba Ultrasound instrument (Power Vision Toshiba SSH-380 ultrasound system, Toshiba American Medical Systems, Carrollton, TX), using a 7.5 MHz linear array transducer. Images were recorded at the common carotid, carotid bulb (bifurcation), and internal carotid arteries bilaterally according to previously developed protocols for the Atherosclerosis Risk in Communities study.²¹ Images were recorded on super VHS video tapes and read by certified readers from the Vascular Ultrasound Research Laboratory in Wake Forest Medical Center, North Carolina, using a semi automatic ultrasound imaging. The maximum carotid IMT readings of left and right far walls were averaged for each segment; if bilateral images could not be obtained, one side was used as the average. Then the averaged carotid IMT of common, bulb, and internal segments was calculated as mean carotid IMT. Common carotid IMT, carotid bulb IMT, internal carotid IMT and the mean carotid IMT were used for analyses. Based on repeated measures of 75 study subjects, the intraclass correlation coefficients for repeat scans were 0.72 for the common carotid, 0.69 for the carotid bulb, and 0.80 for the internal carotid.

All data analyses were performed using SAS version 9.1. HOMA-IR and TG/HDL-C were log-transformed to improve the normality of distribution for correlation and regression analyses; however, their mean values in original scales were presented in Table 1 for description. Differences in mean values of study variables between race-sex groups as well as serum phosphorus between smokers and nonsmokers were tested by analysis of covariance models. The correlation of the serum phosphorus with CV risk factor variables and carotid IMT was assessed using Pearson correlation coefficients. The independent relation of serum phosphorus on carotid IMT was examined by multivariate regression models, adjusting for other CV risk factor variables and eGFR; because cigarette smoking, which contains substantial amounts of nicotine, free radicals and prooxidants to produce oxidative stress²² and higher serum phosphorus,^{23,24} may confound the results, two separate models without (model I) and with (model II) smoking status were used. Further, the interaction of serum phosphorus and smoking on carotid IMT was tested by including an interaction term.

Results

Table 1 shows levels of study variables by race and sex. Significant racial differences were noted for phosphorus (blacks>whites), carotid IMT (black females>white females), BMI (black females>white females), HOMA-IR (black females>white females), TG/HDL-C (whites>blacks), LDL-C (white females>black females), MAP (blacks>whites), eGFR (blacks>whites) and number of smokers (black males>white males). Sex-related difference were significant for carotid IMT (males>females), BMI (white males>white females and black females>black males), HOMA-IR (white males>white females and black females>black males), TG/HDL-C (males>females), LDL-C (males>females), MAP (males>females), eGFR (black females>black males) and number of smokers (black males>black females).

Pearson correlation coefficients of serum phosphorus with carotid IMT and CV risk factor variables are presented in Table 2. Serum phosphorus was significantly correlated with carotid IMT, adjusting for race, sex and age. Importantly, smokers had significantly higher mean levels ($\pm\text{SD}$) of serum phosphorus (3.52 ± 0.54 mg/dL) than nonsmokers (3.41 ± 0.56

mg/dL), adjusting for race, sex and age ($p=0.008$). In addition, serum calcium levels did not show significant relationship with carotid IMT (data not shown).

Regression coefficients of carotid IMT on serum phosphorus and CV risk factor variables are presented in Table 3. In model I (without smoking status), sex (male>female), age, Log-TG/HDL-C, LDL-C, MAP and phosphorus were significantly and positively associated with carotid IMT. In model II, which included smoking status, serum phosphorus was still significantly associated with carotid IMT along with other variables retained in model I. In addition, smoking was significantly associated with carotid IMT in model II. In addition to the mean carotid IMT, we also examined the relationship of phosphorus to carotid IMT of individual segments. Serum phosphorus was significantly associated with common carotid IMT ($p<0.001$), carotid bulb IMT ($p=0.006$) and internal carotid IMT ($p=0.010$) with CV risk factor variables included in the models.

The interaction effect of serum phosphorus with smoking on carotid IMT was tested in an interaction regression model as shown in Figure 1. Carotid IMT increased with increasing quartiles of serum phosphorus in both smokers and nonsmokers; however, the increasing trend in smokers was significantly greater than that in nonsmokers ($p=0.019$ for interaction). In order to examine the synergistic effect of nicotine intake on the phosphorus-IMT relationship, the interaction effect between number of cigarettes per day and serum phosphorus (as a continuous variable) was also tested. The interaction effect on carotid IMT was significant ($p=0.002$). Further, in a subset of nonsmokers ($n=431$) who did not have hypertension, dyslipidemia and diabetes, a similar but nonsignificant trend of association of phosphorus with carotid IMT ($\beta=0.009$, $p=0.416$) was noted.

Discussion

The present study demonstrates that increasing levels of serum phosphorus, even within the normal range, are positively and independently related to subclinical atherosclerosis, measured as carotid IMT. Furthermore, when estimated glomerular filtration rate derived from the Modification of Diet in Renal Disease study equation¹⁹ was added to the multivariate regression model, serum phosphorus, but not estimated glomerular filtration rate, was still significantly related to carotid IMT in these younger adults without kidney disease (data not shown). This is consistent with earlier findings on a relatively older population.¹¹ These findings based on a community-dwelling cohort of younger asymptomatic adults, free of selection bias, are noteworthy in that they underscore the potential value of phosphorus as a risk factor for CV risk in younger population.

Another interesting finding of this study is that the smoking-serum phosphorus interaction was significant and synergetic, with the magnitude of relationship between phosphorus and carotid IMT in smokers vs nonsmokers being significantly stronger. Furthermore, nicotine intake measured as number of cigarettes smoked per day also showed a significant synergistic effect on the phosphorus-IMT relationship. Little comparable data are available in the literature for comparison in this regard. Deleterious effect of smoking on arterial wall properties is attributed to vasoactive substances including carbon monoxide, reactive oxygen species and nicotine related to adverse changes in vascular reactivity, as reflected by impaired basal production of nitric oxide.²² Of note, the current observation showing higher phosphorus levels in smokers vs nonsmokers is consistent with the earlier finding in smokers²³ and experimentally with rats treated with nicotine.²⁴ Furthermore, in our study the phosphorus-carotid IMT association became not significant, although the trend was similar, in a subset of nonsmokers without hypertension, dyslipidemia and diabetes, indicating that the effect of phosphorus on carotid IMT may also depend on other CV risk factors.

Although hyperphospheremia is considered a risk factor for CV disease, especially among those with chronic kidney disease, the underlying mechanism(s) linking excess serum phosphorus within normal range to subclinical and overt CV disease in individuals with normal kidney function is not well understood. Based on the research findings on individuals with normal kidney function, the possible mechanisms may include, among others, promotion of vascular calcification by inducing phenotypic alteration of smooth muscle cells into osteoblast/chondrocyte-like cells,²⁵ induction of synthesis of inflammatory cytokine interleukin-6 by increasing circulating parathyroid hormone,^{26,27} and down regulation of 1,25-dihydroxyvitamin D production and related increase of coronary calcification and risk of myocardial infarction.^{28,29} It should be emphasized that although excess serum phosphorus and the attendant CV risk may be due to subclinical renal dysfunction and secondary hyperparathyroidism, such a pathogenic pathway may not be likely to explain the observed relationship in this younger adult study cohort with normal kidney function. Further studies in this direction are obviously needed in the general population having serum phosphorus levels within the normal range.

As a limitation, the cross-sectional nature of this observational study cannot address the issue of causality but only suggest putative mechanism(s) as discussed above. Further, the present study did not assess the determinants of serum phosphorus levels including the parathyroid hormone, vitamin D levels and dietary phosphorus intake.

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Figure 1.
The relationship of carotid intima-media thickness (IMT) to smoking status and serum phosphorus quartiles specific for race, sex and age: The Bogalusa Heart Study

Table 1

Levels of study variables by race and sex

Variable *	White		Black		P Value for difference	
	Male (n=377)	Female (n=479)	Male (n=144)	Female (n=210)	Race	Sex
Age (years)	36 ± 4	36 ± 5	36 ± 4	35 ± 5	NS	NS
Body mass index (kg/m ²)	29 ± 6	28 ± 7	29 ± 7	31 ± 8	<0.001 [†]	<0.05
Homeostasis model assessment of insulin resistance	3.0 ± 3.0	2.4 ± 2.2	2.8 ± 2.6	3.6 ± 5.5	<0.001 [†]	<0.05
Triglycerides/High-density lipoprotein cholesterol	4.5 ± 4.7	2.8 ± 3.6	3.1 ± 3.6	1.8 ± 1.1	<0.001	<0.001
Low-density lipoprotein cholesterol (mg/dL)	130 ± 34	124 ± 33	125 ± 43	114 ± 30	<0.002 [†]	<0.05
Mean arterial pressure (mm Hg)	93 ± 8	87 ± 9	99 ± 13	92 ± 12	<0.001	<0.001
Smoker (%)	29	28	42	29	<0.001 [‡]	<0.05 [§]
Estimated glomerular filtration rate (mL/min/1.73m ²)	97 ± 16	98 ± 22	105 ± 20	116 ± 25	<0.001	<0.001 [§]
Phosphorus (mg/dL)	3.35 ± 0.54	3.37 ± 0.52	3.70 ± 0.59	3.61 ± 0.55	<0.001	NS
Carotid intima-media thickness (mm)	0.85 ± 0.18	0.75 ± 0.12	0.87 ± 0.16	0.79 ± 0.14	<0.001 [†]	<0.001

* Means ± SD for continuous variables

NS indicates p>0.05;

[†] females only;

[‡] males only;

[§] blacks only

Table 2

Correlations of serum phosphorus levels with cardiovascular risk factor variables and carotid intima-media thickness

	r	p-value
Age [*]	-0.014	0.599
Body mass index [†]	0.009	0.765
Log-Homeostasis model assessment of insulin resistance [†]	-0.040	0.170
Log-Triglycerides/High-density lipoprotein cholesterol [†]	-0.017	0.559
Low-density lipoprotein cholesterol [†]	0.028	0.333
Mean arterial pressure [†]	0.041	0.153
Estimated glomerular filtration rate [†]	0.034	0.244
Carotid intima-media thickness [†]	0.124	<0.001

^{*} adjusted for race and sex

[†] adjusted for race, sex and age

Table 3

Regression coefficients of carotid intima-media thickness on serum phosphorus levels and cardiovascular risk factor variables

Predictor variable	Model I		Model II	
	β	p-value	β	p-value
Black race	0.017	0.080	0.016	0.115
Male sex	0.057	<0.001	0.057	<0.001
Age	0.010	<0.001	0.010	<0.001
Body mass index	0.001	0.473	0.001	0.263
Log-Homeostasis model assessment of insulin resistance	0.003	0.671	0.007	0.359
Log-Triglycerides/High-density lipoprotein cholesterol	0.018	0.005	0.015	0.025
Low-density lipoprotein cholesterol	0.001	<0.001	0.001	<0.001
Mean arterial pressure	0.002	<0.001	0.002	<0.001
Estimated glomerular filtration rate	0.0003	0.104	0.0002	0.200
Smoking (yes/no)	-----	-----	0.032	<0.001
Phosphorus	0.030	<0.001	0.028	<0.001
R ²	0.262		0.270	