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ORIGINAL STUDY

Serum phosphorus levels are associated with carotid intima-media thickness in asymptomatic postmenopausal women

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Abstract

Objective: Serum phosphorous is a significant risk factor for increased carotid intima-media thickness. Increased thickness of the carotid intima is a known cause of cardiovascular disease. Coronary heart disease is a significant cause of mortality and morbidity in postmenopausal women. This study aimed to compare the relationship between serum phosphorous concentration and carotid intima-media thickness in healthy asymptomatic postmenopausal women.

Methods: A retrospective review of the medical records from a health checkup center in Gangnam Severance hospital between March 2007 and September 2017 was conducted. We examined asymptomatic postmenopausal female patients with age range between 56 and 66 ($N = 361$) who underwent measurement of carotid intima-media thickness by B-mode ultrasonography. The physiological variables analyzed included mean blood pressure, body mass index, renal function (serum creatinine and estimated glomerular filtration rate), cholesterol levels (total cholesterol, triglyceride, and high- and low-density lipoprotein), serum phosphorous, calcium, electrolytes, diabetic status, hypertension, and albumin.

Results: Pearson correlation test showed that carotid intima-media thickness was significantly associated with age ($r = 0.192$, $P < 0.001$), mean blood pressure ($r = 0.116$, $P = 0.029$), diastolic blood pressure ($r = 0.146$, $P = 0.029$), serum phosphorous ($r = 0.134$, $P = 0.012$), and lactate dehydrogenase ($r = 0.106$, $P = 0.047$). On the basis of age-adjusted multivariate linear regression analysis, carotid intima-media thickness was significantly correlated with serum phosphorous levels ($\beta = 0.273$, $P = 0.022$) in asymptomatic menopausal women. Increased carotid intima-media thickness (cut-off 1.5 mm) was detected, although serum phosphorous was within the normal range (2.8-4.5 mg/dL).

Conclusions: Serum phosphorus concentration is significantly associated with carotid intima-media thickness in asymptomatic menopausal women.

Key Words: Carotid intima-media thickness – Menopause – Phosphorous.

Coronary heart disease is the leading cause of mortality and morbidity in postmenopausal women. A high serum phosphorous level has been associated with increased mortality from cardiovascular disease (CVD) in patients who experience chronic kidney disease.[1,2] Although within the normal range, the serum phosphorous level is indicated as an independent factor of increased mortality risk for patients with CVD.[3] In another study, serum phosphorous levels within the normal range showed a significant correlation with carotid intima-media thickness (CIMT) in asymptomatic young adults. Moreover, the phosphorous levels may be a potentially modifiable risk factor for stroke and death within the general population.[4]

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In a 1960s study, the serum phosphorous levels in men and women differed with progressive aging. From the age of 20 to 60 years, men experience a progressive decrease in serum phosphate levels. Although premenopausal women show a similar decrease in serum phosphate level, the serum phosphate levels increase after menopause.[5] A few studies have elucidated the relationship between serum phosphorous level and coronary heart problems in postmenopausal women.

In this study, we hypothesized that the serum phosphorous concentration is a marker for CVD in asymptomatic postmenopausal women. To identify the factors associated with CIMT, we compared the relationship between serum phosphorous levels and CIMT in asymptomatic postmenopausal women compared with physiological functions. This study aimed to determine the effects of altered serum phosphorus levels on cardiovascular events in postmenopausal women. The carotid artery intima-media thickness is a validated indicator of subclinical atherosclerosis and future CVD risk.[6-8]

METHODS

Patients

A retrospective review of the medical records of asymptomatic postmenopausal female patients with age range between 56 and 66 ($N = 361$) who were not diagnosed with coronary heart disease or a metabolic disorder such as hypo/hyperparathyroidism previously was conducted. The measurements of CIMT by B-mode ultrasonography were recorded between March 2007 and September 2017 for all routine health checkups at Gangnam Severance Hospital, Korea. All women signed informed consent forms. This retrospective study was conducted in accordance with the ethical standards of the Helsinki Declaration and was approved by the institutional review board of Yonsei University Health System, Gangnam Severance Hospital. Of the 361 eligible participants, 4 patients were excluded due to missing information and another 4 were excluded due to errors in recording their age at the onset of menopause. Thus, a total of 353 participants were included without any missing data in the study.

Carotid ultrasonography

The carotid arteries were evaluated by a standardized protocol.[9] The ultrasonographic images were acquired in end diastole (defined as the R wave of an electrocardiogram) by sonographers certified by the Registry of Diagnostic Cardiac Sonographers, and they were equipped with an 11 MHz imaging transducer (iU22 or EPIQ 5 [Philips, Andover, MA]). With the participants in the supine position and with slight hyperextension of the neck, the common carotid artery, internal carotid artery, and external carotid artery including carotid bulb and vertebral arteries were identified. All carotid measurements were performed using a semiautomated vessel-wall detection software. Following short-axis 2D image acquisition of the common carotid artery (CCA), long-axis B-mode ultrasound images were acquired for subsequent measurements. Carotid measurements included intima-media thickness of the far vessel wall at a site approximately 1 cm proximal to the carotid bulb. The averaged intima-media thickness (IMT) values of the left and right CCAs were subsequently used in all analyses. Plaque was defined as protrusion of the vessel wall into the arterial lumen of at least 0.5 mm, with an IMT 50% of the IMT of the surrounding sites or an IMT >1.5 mm. The peak systolic velocity and end diastolic velocity were measured in the CCA, external carotid artery, and internal carotid artery using a semiautomatic analysis system.

Other variables

The participants were instructed to fast for 8 to 10 hours before screening, and compliance was determined by an interview before examination. Height and weight were measured twice. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Blood pressure was measured using mercury sphygmomanometers on the right arm of the participants in a relaxed sitting position by two randomly assigned nurses (three replicates each). The first and fifth Korotkoff sounds were used to determine the systolic (sBP) and diastolic blood pressure (dBP), respectively. The mean blood pressure (MBP) was estimated as a function of the sBP and dBP [(sBP + 2 dBP)/3]. The serum phosphorous levels were measured using the ammonium molybdate method, as part of the multiple chemistry profile (SMA 20) using the multichannel Olympus Au-5000 Analyzer (Olympus, Lake Success, NY). The serum levels of cholesterol and triglycerides were determined enzymatically on a Hitachi 902 Automatic analyzer (Roche Diagnostics, Indianapolis, IN). The chemistry tests including fasting glucose, creatinine, uric acid, blood urea nitrogen, serum calcium, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, lactate dehydrogenase (LDH), and gamma glutamyl transferase were measured using Atellica CH 930 (Siemens, Erlangen, Germany). The estimated glomerular filtration rate (eGFR) was estimated as a function of age, serum creatinine, sex, and race using the simplified modification of diet in renal disease equation: (mm/min/1.73 m^2) = 186.3 × creatinine −1.154 × age −0.203 × (0.742 if the patient was a woman) × (1.21 if the patient was of African descent), where m^2 denotes the body surface area in square meters.

Statistical analysis

Continuous or categorical variables were described as mean ± standard deviation or number percentage. The age adjusted correlation of continuous variables was examined by the partial Pearson correlation coefficient test. A multivariable stepwise regression analysis was performed to find the independent CIMT predictors, including 15 variables; age, MBP, BMI, phosphorous, uric acid, aspartate aminotransferase (AST), LDH, low-density lipoprotein, estimated glomerular filtration rate, number of births, smoking history, hypertension, diabetes mellitus, history of cancer, and history of hormonal treatment. The null hypothesis was rejected for $P < 0.05$.

TABLE 1. *Baseline characteristics in postmenopausal women*

Variables ($N = 353$)	Mean ± SD or number (%)
Age, y	61.45 ± 7.41
Menopause age, y	50.22 ± 4.25
Menopausal duration, y	11.24 ± 7.89
Menarche age, y	14.20 ± 0.75
BMI, kg/m^2	24.04 ± 4.02
Mean blood pressure, mmHg	94.74 ± 11.56
Systolic blood pressure, mmHg	129.4 ± 16.7
Diastolic blood pressure, mmHg	77.41 ± 10.13
No. pregnancies	1.57 ± 2.21
No. births	1.05 ± 1.36
No. abortions	0.67 ± 1.24
History of alcohol	100 (28.3%)
Smoker	18 (5.1%)
Regular exercise	230 (65.2%)
Thyroid disease	94 (26.6%)
Hypertension	129 (36.5%)
Diabetes mellitus	22 (6.2%)
History of hysterectomy	18 (5.1%)
History of cancer	22 (6.2%)
Hormonal treatment	44 (12.5%)
Carotid intima-media thickness (mm) maximum value	1.56 ± 1.6

BMI, body mass index; No., number; SD, standard deviation.

111All computations relied on standard software (SPSS v23; SPSS Inc [IBM], Chicago, IL).

RESULTS

A total of 353 women were analyzed. The mean age was 61.45 ± 7.41 years, whereas the mean BMI was 24.04 ± 4.02 kg/m^2 and the MBP was 94.74 ± 11.6 mmHg. There were 129 women (36.5%) with hypertension and 22 women (6.2%) with diabetes mellitus. The mean maximum CIMT was 1.56 ± 1.6 mm (Table 1). The biochemical characteristics are shown in Table 2. The mean total cholesterol and low-density lipoprotein cholesterol levels were 211.6 ± 41.26 and 136.07 ± 38.5 mg/dL, respectively. The mean eGFR was 94.44 ± 12.8 mL/min/1.73 m^2; serum uric acid level, 4.67 ± 1.04 mg/dL; serum phosphorus level, 3.98 ± 0.7 mg/dL; and serum calcium level, 9.23 ± 0.43 mg/dL. The AST and LDH levels were 27.38 ± 14.37 and 384.17 ± 71.69 IU/L, respectively (Table 2).

TABLE 2. *Biochemical characteristics in postmenopausal women*

Variables ($N = 353$)	Mean ± standard deviation
Total cholesterol, mg/dL	211.6 ± 41.3
TG, mg/dL	128.98 ± 68.7
HDL, mg/dL	56.77 ± 13.0
LDL, mg/dL	136.07 ± 38.5
Fasting glucose	101.96 ± 16.5
eGFR, mL/min/1.73 m^2	94.44 ± 12.8
Serum creatinine, mg/dL	0.66 ± 0.14
BUN, mg/dL	14.52 ± 3.3
Uric acid, mg/dL	4.67 ± 1.0
Phosphorous, mg/dL	3.98 ± 0.7
Calcium, mg/dL	9.23 ± 0.4
Total protein, g/dL	7.28 ± 0.4
Albumin, mg/dL	4.59 ± 0.3
Total bilirubin, mg/dL	0.78 ± 0.3
Alkaline phosphatase	77.86 ± 22.9
AST, IU/L	27.38 ± 14.4
Gamma GT	24.03 ± 18.3
LDH, IU/L	384.17 ± 71.7

AST, aspartate aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GT, glutamyl transferase; HDL, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL, low-density lipoprotein cholesterol; TG, triglyceride.

TABLE 3. *Pearson correlation analysis of the carotid intima-media thickness with the covariates*

Variables	Pearson correlation coefficient	P
Age, y	0.192	<0.001[a]
Menopause age, y	0.023	0.667
Menopausal duration, y	−0.023	0.667
Menarche age, y	0.002	0.970
BMI, kg/m^2	−0.060	0.258
Mean blood pressure, mmHg	0.116	0.029[b]
Systolic blood pressure, mmHg	0.063	0.239
Diastolic blood pressure, mmHg	0.146	0.029[b]
Total cholesterol	0.020	0.707
TG, mg/dL	0.021	0.689
HDL, mg/dL	−0.022	0.680
LDL, mg/dL	0.022	0.680
Fasting glucose, mg/dL	0.029	0.593
eGFR, mL/min/1.73 m^2	−0.022	0.684
Phosphorous, mg/dL	0.134	0.012[b]
Uric acid, mg/dL	0.082	0.125
Calcium, mg/dL	0.002	0.970
Total protein, g/dL	0.079	0.137
Albumin, mg/dL	0.064	0.230
Total bilirubin, mg/dL	0.002	0.966
Alkaline phosphatase, IU/L	0.032	0.554
AST, IU/L	0.099	0.063
Gamma GT, IU/L	−0.029	0.586
LDH, IU/L	0.106	0.047[b]

AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; GT, glutamyl transferase; HDL, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL, low-density lipoprotein cholesterol; TG, triglyceride.
[a]Except for age, the other variables were adjusted for age to analyze with CIMT by Pearson correlation.
[b]Statistically significant, $P < 0.05$.

The analysis of Pearson correlations between the mean CIMT and clinical parameters showed that age ($r = 0.192$, $P < 0.001$), MBP ($r = 0.116$, $P = 0.029$), dBP ($r = 0.146$, $P = 0.029$), serum phosphorus level ($r = 0.134$, $P = 0.012$), and serum LDH level ($r = 0.106$, $P = 0.047$) were significantly associated with the mean CIMT (Table 3).

The univariate regression analysis results are shown in Table 4. Age, MBP, serum phosphorous level, LDH level, eGFR, and a history of hormonal treatment were associated with CIMT; these associations were clinically significant. In multivariate regression analysis, age ($\beta = 0.038$, $P = 0.001$), MBP ($\beta = 0.021$, $P = 0.004$), serum phosphorus level ($\beta = 0.273$, $P = 0.022$), serum AST level ($\beta = 0.012$, $P = 0.034$), and a history of hormonal treatment ($\beta = 0.609$, $P = 0.014$) were significant and independent explanatory variables for the mean CIMT. The adjusted R^2 and Akaike information criterion were 0.09 and 1302.1, respectively (Table 4).

The scatter plot in Figure 1 shows a positive correlation between CIMT and serum phosphorous level. The serum phosphorous level was 3.7 mg/dL for a CIMT of 1.5 mm.

TABLE 4. *Linear regression analysis results (univariate and multivariate analysis)*

Variable	Univariable		Multivariable	
	Estimate (SE)	*P*	Estimate (SE)	*P*
Age, y	0.041 (0.011)	<0.001	0.038 (0.011)	0.001
Mean blood pressure, mmHg	0.021 (0.007)	0.005	0.021 (0.007)	0.004
BMI, kg/m^2	−0.011 (0.021)	0.609	−0.040 (0.021)	0.059
Phosphorous, mg/dL	0.254 (0.122)	0.038	0.273 (0.119)	0.022
Uric acid, mg/dL	0.146 (0.081)	0.071		
AST, IU/L	0.011 (0.006)	0.066	0.012 (0.006)	0.034
LDH, IU/L	0.003 (0.001)	0.005		
LDL, mg/dL	0.000 (0.002)	0.859		
eGFR, mL/min/1.73 m^2	−0.013 (0.007)	0.050		
No. births	0.100 (0.062)	0.104	0.095 (0.062)	0.129
Smoker	0.367 (0.382)	0.338		
Hypertension	0.251 (0.174)	0.151		
Diabetes mellitus	0.217 (0.348)	0.533		
History of cancer	−0.345 (0.348)	0.321	−0.529 (0.342)	0.123
Hormonal treatment	0.548 (0.253)	0.031	0.609 (0.246)	0.014
			Adjusted R^2 0.09, AIC: 1302.1	

AIC, Akaike information criterion; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; No., number.

DISCUSSION

In humans, serum phosphorous and calcium play important roles in energy production, storage, and signaling.[10] The increase in the levels of minerals in the extracellular space affect the vascular smooth muscle cells. This can lead to atherosclerosis and vascular calcification.[11] Among noninvasive image analysis, CIMT is well-known as an indicator and surrogate of cardiovascular health status. CIMT has emerged as an important tool for the prediction of cardiovascular and stroke risk stratification because it is precisely reflective of atherosclerosis, which is associated with future cardiovascular and stroke events.[4,6,8,12-14]

When women become menopausal, the estrogen levels decrease rapidly; therefore, the associated risk of progression to subclinical atherosclerosis can increase in these women, as suggested in the studies by Lerner et al.[15]

Previous studies have reported that CIMT is significantly correlated with serum phosphorous level; an increased serum phosphorus level is a well-known indicator of increased risk for ischemic stroke.[4,16] Our results were similar to those of several previous studies because CIMT was significantly associated with serum phosphorous level after adjusting for age.

As age increases, serum phosphorous level changes. In our data analysis, we performed Pearson correlation analysis by

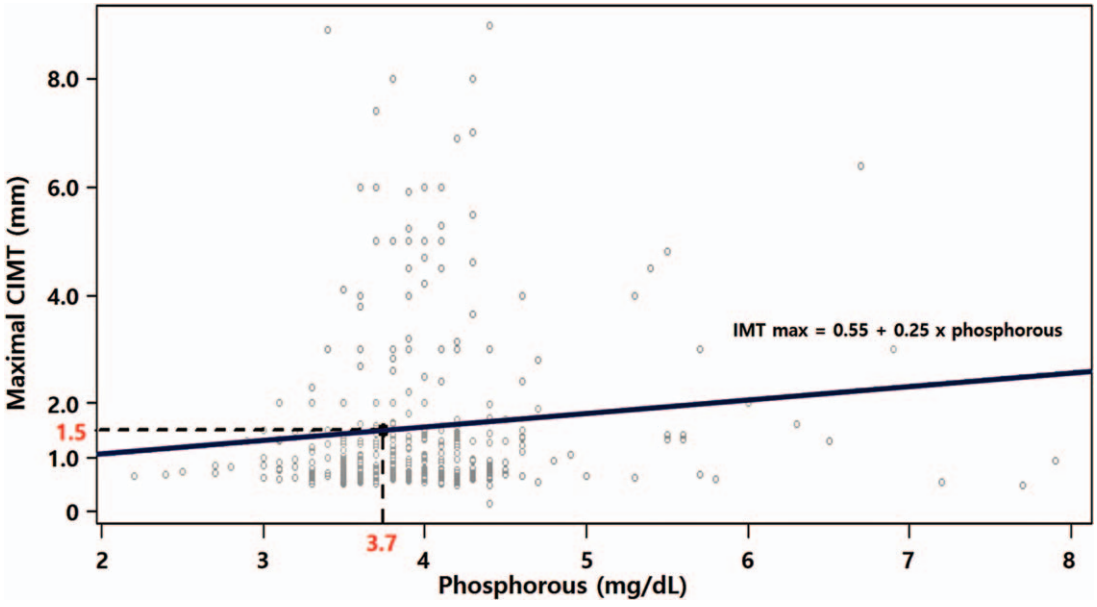

FIG. 1. Correlation scatter plot between CIMT and serum phosphorous levels. CIMT, carotid intima-media thickness.

adjusting for age. The age-adjusted results showed that the serum phosphorous level was significantly associated with CIMT as well as with MBP, dBP, and serum LDH levels.[17,18]

Based on the results of a previous study, the CIMT cut-off for atherosclerosis is determined as 1.5 mm. When the CIMT is greater than 1.5 mm, the hazard ratio increases to more than two times above the baseline.[19,20] In our study, a correlation scatter plot showed that at a CIMT of 1.5 mm, the serum phosphorous level was 3.7 mg/dL, which is classified within the normal serum phosphorous levels (normal range: 2.8-4.5 mg/dL). In asymptomatic postmenopausal women, even when the serum phosphorous levels are within the normal range, cardiac disease should be suspected for serum phosphorous levels greater than 3.7 mg/dL.

LIMITATIONS

There are some limitations of our study. First, the data were collected retrospectively with only data from a single health center. Moreover, the sample size was small, and long-term follow-up data were not included. Data for cardiovascular events were also not collected. In future studies, we aim to achieve statistical power, which can confirm cardiovascular events, by collecting long-term follow-up data continuously.

Previous studies have reported that CIMT decreased in patients undergoing hormonal treatment.[21,22] Our data, however, showed the opposite trend, because only 12.5% of the women included in the study received hormonal treatment. Therefore the results of the study cannot be generalized.

CIMT is known to be affected by several factors. In our study, the predicting value is 9%, which shows a relatively low prediction rate.

CONCLUSIONS

This is the first study to report the association between serum phosphorous levels and CIMT in asymptomatic postmenopausal women. Our study identified the factors that relate to the variation of CIMT, which is related to cardiovascular risk. Age, MBP, serum phosphorus level, serum AST level, and a history of hormonal treatment were significantly associated with CIMT. In asymptomatic menopausal women, even when the serum phosphorous levels are within the normal range, cardiac disease should be suspected at levels above 3.7 mg/dL.

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