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Valve Disease

Association of Serum Phosphate Levels With Aortic Valve Sclerosis and Annular Calcification

The Cardiovascular Health Study

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Objectives This study was conducted to evaluate mineral metabolism markers as potential risk factors for calcific aortic valve disease.

Background Mineral metabolism disturbances are common among older people and may contribute to cardiac valvular calcification. Associations of serum mineral metabolism markers with cardiac valvular calcification have not been evaluated in a well-characterized general population of older adults.

Methods We measured serum levels of phosphate, calcium, parathyroid hormone, and 25-hydroxyvitamin D in 1,938 Cardiovascular Health Study participants who were free of clinical cardiovascular disease and who underwent echocardiographic measurements of aortic valve sclerosis (AVS), mitral annular calcification (MAC), and aortic annular calcification (AAC). We used logistic regression models to estimate associations of mineral metabolism markers with AVS, MAC, and AAC after adjustment for relevant confounding variables, including kidney function.

Results The respective prevalences of AVS, MAC, and AAC were 54%, 39%, and 44%. Each 0.5 mg/dl higher serum phosphate concentration was associated with greater adjusted odds of AVS (odds ratio [OR]: 1.17, 95% confidence interval [CI]: 1.04 to 1.31, $p = 0.01$), MAC (OR: 1.12, 95% CI: 1.00 to 1.26, $p = 0.05$), and AAC (OR: 1.12, 95% CI: 0.99 to 1.25, $p = 0.05$). In contrast, serum calcium, parathyroid hormone, and 25-hydroxyvitamin D concentrations were not associated with aortic or mitral calcification.

Conclusions Higher serum phosphate levels within the normal range were associated with valvular and annular calcification in a community-based cohort of older adults. Phosphate may be a novel risk factor for calcific aortic valve disease and warrants further study. (J Am Coll Cardiol 2011;58:291–7) © 2011 by the American College of Cardiology Foundation

Calcific aortic valve disease (CAVD) is a progressive condition involving calcification and fibrosis of the aortic valve leaflets. The disease sequence begins with aortic valve sclerosis (AVS), in which the leaflets thicken and develop microcalcification but do not obstruct left ventricular outflow. Progressive calcification and fibrosis result in obstruction to left ventricular outflow, which characterizes clinical aortic stenosis. Both aortic sclerosis and aortic stenosis are common among older people (1) and share histological and epidemiological features with atherosclerosis (2–4). However, unlike atherosclerosis, there is no known effective

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Abbreviations and Acronyms

25-OHD = 25-hydroxyvitamin D

AAC = aortic annular calcification

AVS = aortic valve sclerosis

CAVD = calcific aortic valve disease

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

LDL = low-density lipoprotein

MAC = mitral annular calcification

PTH = parathyroid hormone

medical therapy for CAVD, and a recent large randomized clinical trial of lipid-lowering therapy failed to reduce the progression of aortic stenosis (5). Identification of novel, modifiable risk factors remains an essential next step in developing medical therapies for valvular heart disease.

Disturbances in mineral metabolism are common among older adults (6,7), and preliminary evidence suggests a potential role in the pathogenesis of cardiac valve calcification. In the setting of kidney disease, in which phosphate metabolism is grossly disturbed, higher serum phosphate concentrations are associated with aortic and mitral valve calcification (8,9). Moreover, primary hyperparathyroidism is linked with aortic valve calcification (10), and vitamin D receptor polymorphisms are associated with aortic stenosis (11). These connections have not yet been evaluated in a general population of older people without known kidney impairment or hyperparathyroidism.

We tested the hypotheses that serum concentrations of phosphate, parathyroid hormone, and 25-hydroxyvitamin D (25-OHD) would be associated with AVS, mitral annular calcification (MAC), and aortic annular calcification (AAC) in a population-based cohort of ambulatory older adults.

Methods

Study population. We evaluated participants from the CHS (Cardiovascular Health Study), a prospective population-based cohort study of cardiovascular disease among older adults. Details of the study design have been published previously (12). Briefly, between 1989 and 1990, CHS enrolled 5,201 ambulatory adults age ≥65 years from 4 U.S. communities (Forsyth County, North Carolina; Washington County, Maryland; Sacramento County, California; and Pittsburgh, Pennsylvania). An additional 687 African Americans were enrolled between 1992 and 1993. Exclusions from CHS included the use of a wheelchair, institutionalization, inability to give informed consent, plans to move away from the area within 3 years, or active treatment for malignancy. Each participating center received institutional review board approval, and all individuals gave informed consent.

We studied CHS participants from the 1992 or 1993 examination who had available measurements of mineral metabolism markers, which were performed as a part of a different ancillary study of incident cardiovascular events. Participants were excluded from the cardiovascular events study if they had a preexisting clinical history of any one of the following cardiovascular diseases: coronary artery disease, heart failure, aortic stenosis, stroke, claudication, arrhythmia, or presence of a pacemaker or implantable cardiac defibrillator. Cardiovascular conditions were determined by review of medical records, electrocardiographic findings, and patient questionnaires (13). There were 4,692 individuals who attended the 1992 or 1993 CHS examination. A total of 1,428 participants were excluded because of prevalent cardiovascular disease, 948 because of inadequate serum volume to run the mineral metabolism measurements, and 378 because of not completing an echocardiogram, leaving 1,938 participants for analysis.

Measurements. Mineral metabolism measurements were performed using serum samples collected during the 1992 or 1993 CHS examination. Participants were asked to fast before collection. Samples were stored at the Laboratory for Clinical Biochemistry Research at the University of Vermont using established methods to ensure long-term stability (14) and were assayed at the University of Washington Clinical Nutrition Research Unit Laboratory. Total 25-OHD was measured on a Waters Quattro Micro mass spectrometer (Waters Corp., Milford, Massachusetts) with an interassay coefficient of variation <3.4%. Intact parathyroid hormone (PTH) was quantified with a 2-site immunoassay (Unicel DxI clinical analyzer, Beckman Coulter Inc., Brea, California) with a reference range of 17 to 66 pg/ml. Phosphate levels were determined using a timed-rate colorimetric reaction method with ammonium molybdate at acidic pH and serum nonionized total calcium was measured using indirect potentiometry on a DxC Synchron analyzer (Beckman Coulter Inc.).

Trained CHS study personnel conducted standardized interviews to determine participant demographics, past medical history, lifestyle factors, and medications. Blood pressure was measured in triplicate 5 min apart. Prescription medication use was ascertained from a review of prescription bottle labels by interviewers. Lipid measurements were made at the Laboratory for Clinical Biochemistry Research, and low-density lipoprotein (LDL) levels were calculated using the Friedwalde equation. Estimated glomerular filtration rate (eGFR) was derived from cystatin C measurements using the equation: eGFR = 76.7 × (cystatin C)$^{-1.19}$ (15). Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications. Diabetes was defined by fasting glucose level >7.8 mmol/l (>140 mg/dl) or the use of a diabetic medication.

Echocardiography. Two-dimensional echocardiograms were recorded on videotape using an SSH-160A ultrasound machine (Toshiba America Medical Systems Inc., Tustin, California) during the 1994 or 1995 CHS examination, as detailed previously (16). The echocardiograms were evaluated at a centralized core laboratory (Georgetown University, Washington, DC) by observers blinded to the participants' clinical history.

AVS, MAC, and AAC were defined based on previous CHS studies (17,18). Aortic annulus (AAC) and leaflet calcification (AVS) were considered separate outcomes because of their different cellular components and potential calcification mechanisms. AVS was identified as aortic cusp thickening with normal aortic cusp excursion and a peak trans-aortic valve flow velocity <2.0 m/s. MAC was defined by an intense echocardiograph-producing structure located at the junction of the atrioventricular groove and posterior mitral leaflet on the parasternal long-axis, short-axis, or apical 4-chamber view. The presence of AAC was similarly defined as increased echodensity of the aortic root at the insertions of the aortic cusps. For 167 participants, individual components of the aortic valve evaluation (peak velocity, cusp excursion, or leaflet thickness) were not evaluated or were considered to be abnormal but did not meet the definition of AVS; these individuals were excluded from AVS analyses. There were 16 participants without assessment of MAC and 48 participants without evaluation of AAC who were excluded from analyses of these outcomes.

Statistical analysis. We evaluated mineral metabolism exposure variables continuously and using previously published categories (8). We analyzed AVS, MAC, and AAC as binary outcome variables. We used linear regression to explore associations of covariates with the serum phosphate concentration (Online Tables). We used logistic regression with robust SE to estimate the association of each mineral metabolism variable with the log odds ratio (OR) of each binary outcome. We created nested multivariable models to evaluate an a priori set of potential confounding variables: age, sex, race, eGFR, hypertension, diabetes, smoking, body mass index, LDL cholesterol, high-density lipoprotein cholesterol, statin use, serum calcium levels, and clinic site. Individual serum samples at each clinical site were collected during the same season, thus providing seasonally adjusted estimates. We investigated potential nonlinear associations using cubic spline models for continuous mineral metabolism covariates. There were 11 individuals who self-identified as an ethnicity other than Caucasian or African American; given the small number, these measurements were classified into the Caucasian strata when models were adjusted for race. Because of the high prevalence of AVS in this population, OR did not approximate relative risk well; thus, we additionally calculated adjusted proportions for easier clinical interpretation.

We tested for whether sex, race, eGFR, and/or serum calcium level modified associations of serum phosphorus with study outcomes using the Wald test. Given no statistically significant interactions, these associations are presented as pooled analyses. We conducted a sensitivity analysis by excluding patients with overt hyperphosphatemia (>4.5 mg/dl); this exclusion did not change inferences. All analyses were conducted using Stata version 10.1 (Stata Corp., College Station, Texas).

Results

There were 1,938 individuals with serum phosphate measurements and available echocardiogram data in this analysis. Serum phosphate concentrations were normally distributed, 3.6 ± 0.5 mg/dl. Overt hyperphosphatemia was rare in this cohort. More than 97% of individuals had a serum phosphate level below the upper limit of normal (4.5 mg/dl), and there were only 3 individuals who had a serum phosphate level >5.0 mg/dl. Serum concentrations of 25-OHD and PTH were 25.8 ± 11.7 ng/ml and 56.0 ± 28.8 pg/ml, respectively. Measurements consistent with primary hyperparathyroidism (calcium >10 mg/dl and PTH >65 pg/ml) were found in 25 participants (1%), and 304 individuals (16%) had 25-OHD deficiency (<15 ng/ml).

The average age of the study population was 73.5 years. The majority of participants were Caucasian, and the mean eGFR was 76.6 ml/min/1.73 m^2 (Table 1). Excluded patients without available measurements were more likely to be older and male and have more comorbidities (Online Tables). In multivariable analysis, female sex had the strongest association with serum phosphate levels, which were on average 0.4 mg/dl greater among women. Additionally, LDL cholesterol level correlated directly with the serum phosphate concentration, whereas body mass index, systolic blood pressure, eGFR, and PTH level were correlated inversely.

The respective prevalences of AVS, MAC, and AAC were 54%, 39%, and 44%. In unadjusted and demographic adjusted models, higher serum phosphate concentrations were associated with greater odds of each valvular calcification outcome (Table 2). Associations of serum phosphate levels with AAC no longer reached statistical significance in fully adjusted models. The adjusted prevalences of AVS, MAC, and AAC were 12%, 11%, and 7% greater, comparing participants in the highest (>4.0 mg/dl) versus lowest (≤3.0 mg/dl) serum phosphate level categories. Associations of serum phosphate levels with valve outcomes appeared to be generally linear (Fig. 1).

Serum concentrations of 25-OHD and PTH were not associated with any of the valvular outcomes (Table 3, Fig. 2). There was no association with calcium level and AVS (OR: 0.93, 95% confidence interval [CI]: 0.70 to 1.25), MAC (OR: 1.24, 95% CI: 0.91 to 1.70), or AAC (OR: 1.02, 95% CI: 0.77 to 1.36). Exclusion of participants with primary hyperparathyroidism did not alter these results.

Discussion

In a community-based population of older adults without known cardiovascular disease, higher serum phosphate levels that were elevated, but still within the normal range, were associated with AVS and MAC. Associations of phosphate level with AAC also were observed but did not reach statistical significance after full adjustment. The observed associations were independent of kidney function and PTH, calcium, and 25-OHD levels, all of which play biological roles in phosphate metabolism and calcification. Importantly, associations were not observed

Table 1 Baseline Characteristics of Participants by Serum Phosphate Concentration

Characteristic	Serum Phosphate Concentration ≤3.0 mg/dl (n = 271)	3.1–3.5 mg/dl (n = 657)	3.6–4.0 mg/dl (n = 675)	>4.0 mg/dl (n = 335)
Age, yrs	73.3 ± 4.6	73.5 ± 4.6	73.6 ± 4.4	73.6 ± 4.7
Men	174 (64.2)	246 (37.4)	119 (17.6)	33 (10.9)
Race				
Caucasian	227 (84)	564 (86)	592 (88)	291 (87)
African American	44 (16)	93 (14)	83 (12)	44 (13)
Hypertension	170 (62.7)	360 (54.8)	342 (50.7)	206 (61.5)
Diabetes	39 (14.4)	79 (12.0)	62 (9.2)	34 (10.1)
Smoking (current or past)	153 (56.5)	329 (50.1)	323 (47.9)	146 (43.6)
Medication use				
Antihypertensive	101 (37.3)	265 (40.3)	251 (37.2)	136 (40.6)
Statin	7 (2.6)	20 (3.0)	39 (5.8)	23 (6.9)
BMI, kg/m^2	27.5 ± 4.4	27.1 ± 4.6	26.6 ± 4.8	26.2 ± 4.4
LDL, mg/dl	122.5 ± 31.7	125.7 ± 30.6	130.3 ± 32.9	135.3 ± 33.5
HDL, mg/dl	50.6 ± 13.6	54.7 ± 14.6	56.9 ± 14.0	58.2 ± 15.2
eGFR, ml/min/1.73 m^2	77.7 ± 18.9	76.5 ± 17.2	77.0 ± 17.0	75.4 ± 18.4
Calcium, mg/dl	9.44 ± 0.38	9.47 ± 0.36	9.49 ± 0.32	9.5 ± 0.42
25-OHD, ng/ml	26.3 ± 11.3	25.6 ± 10.1	26.0 ± 12.6	25.4 ± 13.1
PTH, pg/ml	67.8 ± 33.9	57.9 ± 28.7	52.3 ± 24.1	50.5 ± 30.4

Values are mean ± SD or n (%).
BMI = body mass index; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PTH = parathyroid hormone; 25-OHD = 25-hydroxyvitamin D.

between PTH, calcium, or 25-OHD levels and calcification outcomes.

To our knowledge, this study is the first to demonstrate an association between serum phosphate levels and cardiac valve calcification in a population-based cohort without chronic kidney disease (CKD). A previous retrospective cross-sectional study of patients with aortic stenosis found an inverse relationship of phosphorus level with aortic valve area on echocardiogram (19). Similarly, a recent case-control study of referred patients with aortic stenosis had a higher unadjusted level of phosphate than that of age- and sex-matched controls (20). Phosphate levels have been associated with calcification of coronary arteries (21,22) and with incidence of future cardiovas-

Table 2 Association of Serum Phosphate Concentration With Aortic Valve Sclerosis, Mitral Annular Calcification, and Aortic Annular Calcification

	Unadjusted OR (95% CI)	p Value	Model 1* OR (95% CI)	p Value	Model 2† OR (95% CI)	p Value
Aortic valve sclerosis, mg/dl						
≤3.0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
3.1–3.5	1.11 (0.82–1.50)		1.23 (0.91–1.68)		1.23 (0.90–1.70)	
3.6–4.0	1.23 (0.91–1.65)		1.47 (1.07–2.02)		1.46 (1.04–2.05)	
>4.0	1.44 (1.02–2.01)		1.78 (1.23–2.57)		1.64 (1.10–2.43)	
per 0.5	1.12 (1.01–1.23)	0.03	1.20 (1.07–1.33)	0.001	1.17 (1.04–1.31)	0.01
Mitral annular calcification, mg/dl						
≤3.0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
3.1–3.5	1.35 (1.00–1.82)		1.30 (0.95–1.77)		1.39 (1.01–1.93)	
3.6–4.0	1.44 (1.07–1.94)		1.34 (0.97–1.84)		1.31 (0.94–1.85)	
>4.0	1.70 (1.22–2.38)		1.58 (1.11–2.27)		1.62 (1.10–2.38)	
per 0.5	1.16 (1.06–1.30)	0.001	1.13 (1.02–1.26)	0.02	1.12 (1.00–1.26)	0.05
Aortic annular calcification, mg/dl						
≤3.0	1.00 (reference)		1.00 (reference)		1.00 (reference)	
3.1–3.5	1.03 (0.77–1.38)		1.07 (0.79–1.44)		1.06 (0.77–1.45)	
3.6–4.0	1.27 (0.95–1.70)		1.35 (0.99–1.84)		1.28 (0.92–1.78)	
>4.0	1.40 (1.01–1.94)		1.50 (1.05–2.14)		1.32 (0.90–1.92)	
per 0.5	1.14 (1.04–1.25)	0.006	1.17 (1.05–1.29)	0.003	1.12 (0.99–1.25)	0.05

*Adjusted for age, sex, and race. †Adjusted for age, sex, race, eGFR, hypertension, diabetes, smoking, BMI, LDL, HDL, statin use, vitamin D, PTH, calcium, and site.
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

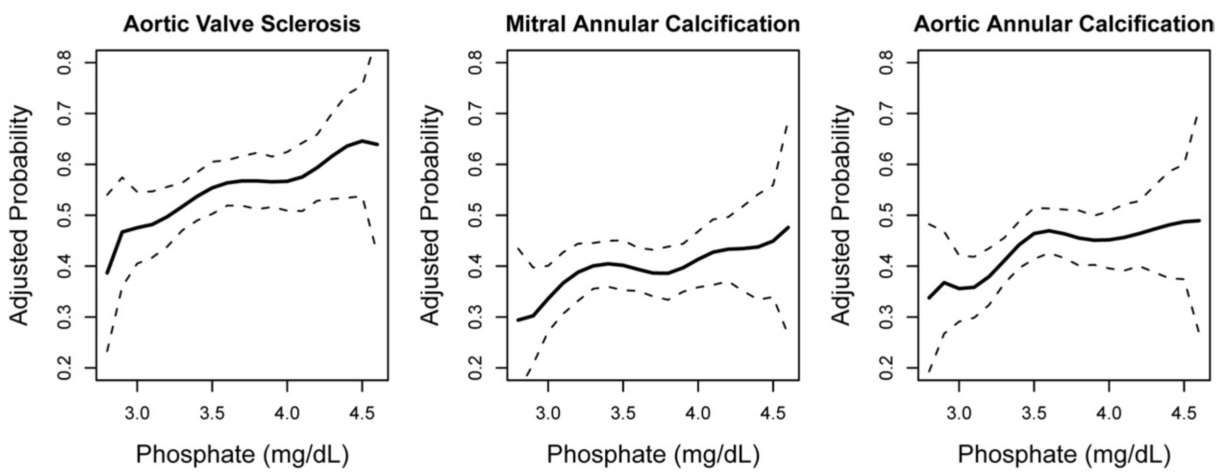

Figure 1 **Association of Phosphate and Valve Calcification**

Fully adjusted cubic splines showing higher prevalence of aortic valve sclerosis, mitral annular calcification, and aortic annular calcification with higher serum phosphate concentrations. **Dashed lines** indicate 95% confidence intervals.

cular events independent of kidney function (23–25) However, none of these previous studies were able to concomitantly measure and adjust for PTH or vitamin D levels.

The odds of aortic sclerosis per SD of phosphate are similar in magnitude to other well-established modifiable risk factors for aortic valve calcification. Stewart et al. (3) previously reported small associations with LDL cholesterol (OR: 1.12, 95% CI: 1.03 to 1.23 [75th vs. 25th percentile]), hypertension (OR: 1.23, 95% CI: 1.1 to 1.4), and smoking (OR: 1.3, 95% CI: 1.1 to 1.7) (3). Similar magnitudes for LDL have been shown in older adults in the Multiethnic Study of Atherosclerosis. Per 1 SD of LDL cholesterol for those age 65 to 74 and 75 to 84 years, the OR of aortic valve calcification was 1.09 and 1.16, respectively (26).

A potential mechanism explaining the relationship between phosphate and cardiovascular disease is dystrophic calcification. Animal models with deletion of the gene for fibroblast growth factor-23, which controls phosphate metabolism, produce phenotypes characterized by hyperphosphatemia, arteriosclerosis, and ectopic cardiac calcification that can be reversed with restrictions in dietary phosphorus (27,28). In vitro studies have shown that phosphate levels within the normal range can trigger osteogenic transformation and mineralization of cultured smooth muscle cells (29). Similar cells that can undergo transdifferentiation into osteoblast-like cells, myofibroblasts, have been identified in the aortic valve interstitial layer (30). In smooth muscle cells, phosphate uptake via the sodium-dependent phosphate cotransporter, Pit-1, has been shown to induce production of osteogenic markers Cbfa1 and osteopontin, both of which have increased gene expression in calcified aortic valves (29,31–33).

This study found a stronger association of phosphate level with AVS as compared with MAC. Conversely, CKD has more often been associated with MAC than with AVS or AAC (8,18,34,35). Mineral metabolism disturbances have been proposed as potential etiologies for valvular and vascular calcification observed in people with CKD. A possible explanation is that, compared with previously

Table 3 **OR (95% CI) of Aortic Valve Sclerosis, Mitral Annular Calcification, and Aortic Annular Calcification by PTH and 25-OHD Levels**

	Aortic Valve Sclerosis		Mitral Annular Calcification		Aortic Annular Calcification	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
PTH, pg/ml						
≤65	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
>65	1.08 (0.87–1.35)	1.21 (0.94–1.56)	0.99 (0.80–1.22)	0.87 (0.68–1.12)	1.01 (0.82–1.25)	0.89 (0.69–1.13)
25-OHD, ng/ml						
≥30	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
15–30	0.93 (0.75–1.16)	0.87 (0.69–1.10)	1.08 (0.88–1.33)	1.00 (0.79–1.26)	1.38 (1.11–1.70)	1.33 (1.06–1.67)
<15	1.04 (0.76–1.42)	0.83 (0.60–1.17)	1.33 (1.01–1.77)	1.21 (0.87–1.69)	1.33 (0.97–1.80)	1.12 (0.81–1.56)

*Adjusted for age, sex, race, eGFR, hypertension, diabetes, smoking, BMI, LDL, HDL, statin use, calcium, and site.
Abbreviations as in Tables 1 and 2.

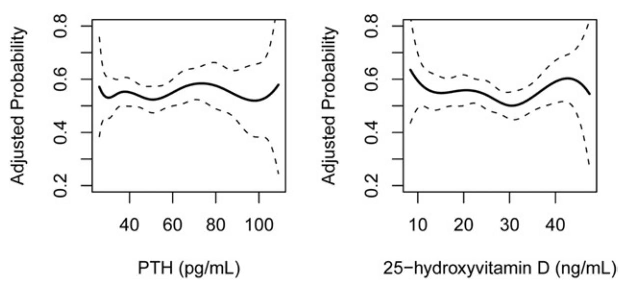

Figure 2 **Fully Adjusted Prevalence of Aortic Valve Sclerosis**

There was no association of parathyroid hormone (PTH) and 25-hydroxyvitamin D levels with aortic valve sclerosis. **Dashed lines** indicate 95% confidence intervals.

studied populations, our population had less kidney disease and no evidence of coronary heart disease. In CKD, mineral disturbances other than phosphate retention and secondary hyperparathyroidism can develop, such as reduction in serum levels of the calcification inhibitor Fetuin-A. Fetuin-A has been shown to correlate inversely with valve calcification in patients receiving dialysis (36). Among patients with coronary heart disease, lower Fetuin-A levels appear to be associated more strongly with MAC than with CAVD (37). We were unable to measure Fetuin-A levels in this study, and the relationship of Fetuin-A with phosphate levels and cardiac calcification remains a topic for future investigation.

We had hypothesized that there may be an association between valve calcification and lower 25-OHD and higher PTH levels. In kidney failure, disturbances in vitamin D metabolism cause secondary hyperparathyroidism, which may accelerate CAVD progression (38). Furthermore, a hospital-based study in patients with unstable angina with preserved kidney function found a significant, although modest, association of more severe CAVD with higher PTH and lower 25-OHD levels (39). High PTH and low vitamin D levels may promote ectopic calcification and inflammation that could lead to cardiovascular disease (40,41). Population-based studies of people without CKD have shown that higher PTH and lower 25-OHD levels are markers for adverse cardiovascular events and are associated with cardiovascular risk factors (42–44) Additionally, 25-OHD levels have demonstrated an inverse association with risk of incident coronary artery calcification (45). It is possible that elevated PTH and inadequate vitamin D levels promote atherosclerosis but not valve calcification. Alternatively, the lack of association in our study may be related to the exclusion of people with known cardiovascular disease.

Study strengths. Strengths of our study include a large sample size from a well-defined community-based cohort with standardized echocardiography measures and risk factor assessment. In addition, we were able to adjust our models for serum cystatin C levels, which more precisely characterize kidney function in older adults than does serum creatinine, the traditional serological marker of eGFR.

Study limitations. First, the study included only single measurements of phosphate, PTH, and 25-OHD, all of which exhibit biological variation over time and all of which were performed 2 years before the echocardiograms. However, these limitations likely would lead to nondifferential misclassification that would attenuate associations toward the null hypothesis. A similar limitation includes not being able to account for dietary phosphate intake in this analysis. However, participants were instructed to fast, and serum phosphate levels are tightly regulated, even in the postprandial state (46,47). Further, because longitudinal echocardiograms were not available, this was a cross-sectional study that reported prevalence, not incidence, of AVS, AAC, and MAC. Additionally, because echocardiograms do not allow precise quantification of calcification severity, relationships of phosphate dose response to calcification severity could not be assessed. Another limitation of this observational study is the possibility that unmeasured confounders might explain observed associations of phosphate with AVS and AAC. Further, phosphate levels were measured only in CHS participants without known cardiovascular disease at year 5, resulting in survival bias in the study population. Finally, because this was an observational study, and not designed to assess the effect of phosphate levels on clinical outcomes, the results should not be used to guide clinical decision making in CAVD.

Conclusions

The findings of this study, along with the role of phosphate in ectopic calcification, suggest that phosphate may be a biologically plausible, novel risk factor for CAVD. If these results are confirmed, they may lead to studies to determine whether novel therapies targeting phosphate metabolism might alter the development or progression of CAVD. Accordingly, the role of phosphate in CAVD warrants further study.

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Key Words: aortic valve ▪ calcification ▪ epidemiology ▪ mitral valve ▪ phosphate.

APPENDIX

For supplemental tables, please see the online version of this article.