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Serum Phosphate and Retinal Microvascular Changes: The Multi-Ethnic Study of Atherosclerosis and the Beaver Dam Eye Study

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Abstract

Purpose—Higher levels of serum phosphate are strongly linked to increased risk of cardiovascular disease and therapies aimed to lower serum phosphate are employed in the management of patients with chronic kidney disease (CKD). Data are limited, however, on serum phosphate as a risk factor for microvascular disease in community-based populations. It is important to determine the impact of novel risk factors, such as phosphate, on the microvasculature.

Methods—We conducted a prospective study of 3919 individuals in the Multi-Ethnic Study of Atherosclerosis (MESA) and 3544 individuals in the Beaver Dam Eye Study (BDES) to test the associations of serum phosphate with retinopathy and retinal vessel caliber, and change in retinopathy severity and change in retinal vessel caliber.

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Supplemental data for this article can be accessed on the publisher's website.

Declaration of interest

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Results—Mean (standard deviation) serum phosphate was 3.66 (0.52) mg/dl in the MESA and 3.77 (0.55) mg/dl in the BDES. In multivariable adjusted models, phosphate was significantly associated with prevalent retinopathy in the MESA (Odds Ratio [OR] per 1 mg/dl increase in phosphate, 1.22; Confidence Interval [CI] 1.02–1.47) and the BDES (OR 1.06; CI 1.01–1.11). In stratified analyses, these relationships were even stronger and only seen in individuals with diabetes in both the MESA (OR 1.81; CI 1.30–2.53) and the BDES (OR 1.16; CI 1.05–1.29). Phosphate was not associated with incident or change in retinopathy severity, nor any retinal caliber outcome.

Conclusions—Among community-living individuals with low prevalence of CKD, higher serum phosphate was associated with prevalent retinopathy in individuals with diabetes. Further longitudinal assessments in patients with diabetes necessitate further investigation.

Keywords

Diabetes; microvascular disease; phosphate; retinopathy

Introduction

Elevated serum phosphate levels, even within the normal range, are implicated in the pathogenesis of vascular disease in patients with and without chronic kidney disease (CKD).^{1–8} Potential mechanisms include induction of vascular calcification in large- and medium-sized vessels and development of endothelial dysfunction.^{9–11} However, there is a paucity of data on the relationships of elevated serum phosphate with microvascular disease. Given that renal microvascular disease is linked to progressive decline in kidney function, cerebral microvascular disease is linked to increased risk of stroke and vascular dementia, and coronary microvascular disease is linked to worse outcomes post cardiac intervention, it is important to determine the impact of novel risk factors, such as serum phosphate, on the microvasculature.^{12,13}

The retinal vascular bed is unique in that it can be easily visualized *in vivo* using noninvasive techniques and presents a distinct opportunity to investigate the impact of different pathogenic processes on microvascular disease.^{14,15} Retinopathy and changes in retinal vessel caliber are associated with renal and cardiovascular disease, even in low risk individuals without diabetes or kidney disease at baseline.^{16–29} We previously demonstrated in individuals with stage 2–4 CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study that higher serum phosphate was significantly associated with more severe retinopathy and greater retinal venular diameter, independent of classic risk factors for retinal vascular disease, such as hypertension and diabetes.¹⁴ However, there are no prospective studies investigating if a higher serum phosphate level is a risk factor for the development or progression of retinopathy or changes in retinal vessel caliber in individuals with or without CKD. In the current study, we tested the hypothesis that higher serum phosphate is associated with the incidence and progression of retinal vascular changes in two large cohorts with low prevalence of CKD.

Materials and methods

Study population

We evaluated cross-sectional and longitudinal associations between serum phosphate concentrations with retinopathy and retinal vessel caliber in individuals who participated in the Multi-Ethnic Study of Atherosclerosis (MESA) and the Beaver Dam Eye Study (BDES). The MESA and BDES are community-based prospective cohort studies that conducted repeated retinal examinations.

The MESA is a prospective cohort study of 6814 men and women of diverse racial and ethnic backgrounds aged 45–85 years at baseline without clinical signs of cardiovascular disease. The primary objective is to investigate risk factors for the incidence and progression of clinical and subclinical cardiovascular disease.³⁰ The baseline MESA examination took place in 2000–2002, at which time serum phosphate levels were measured. Fundus photography was completed at each site and occurred at Exam 2 between August 2002 and January 2004, and follow up fundus photographs were taken again approximately 8 years later in 2010–2012.^{31,32} We conducted a staggered cross-sectional study of 5837 participants with baseline serum phosphate measurements and Exam 2 fundus examinations available. Prospective analyses included 3919 individuals who underwent follow-up fundus examinations approximately 8 years after the initial visit.

The BDES is a prospective study of residents of Beaver Dam, Wisconsin, who are predominately of European ancestry and aged 43–84 years at baseline.³³ The primary objective is to investigate age-related eye diseases longitudinally in 4926 individuals. The baseline BDES examination took place during 1988–1990, at which time serum phosphate and baseline fundus examinations were completed.³³ We conducted a cross-sectional study of 4784 BDES participants to investigate the association of serum phosphate with prevalent retinopathy. Our prospective study included 3544 participants who had year 5 fundus examinations, which occurred between 1993 and 1995.³⁴

All participants provided written and informed consent prior to examinations. All sites in the MESA and BDES received institutional review board approval and followed the principles of the Declaration of Helsinki.

Exposures

Serum phosphate was our primary exposure. Fasting blood samples were obtained in all the MESA participants at baseline and stored at -80°C . Serum phosphate was measured in first use samples shipped to the University of Washington using a time-rated colorimetry method.³⁵ In the BDES, non-fasting blood samples were obtained at the baseline examination, and serum phosphate was measured after formation of a phosphomolybdate complex using a RZ-XT Technicon random access chemistry analyzer (Technicon Instruments Corporation, Tarrytown, NY, USA).³⁶

Retinal photography

Investigators followed standard protocols to perform fundus photography in the MESA and BDES, as previously described.^{31,33} In the MESA, after participants sat in a darkened room to induce physiologic pupillary dilation, two photographs of each eye were taken using a 45°, 6.3 megapixel, digital, non-mydriatic camera.³⁷ One photograph centered on the fovea, while the other photograph centered on the optic disc. Photographs were sent to the Ocular Epidemiology Reading Center at the University of Wisconsin in Madison, Wisconsin, where trained graders, who were masked to all participant characteristics, evaluated images for retinopathy features and completed retinal vessel measurements.³¹ In the BDES, after pharmacologic dilatation of the pupils, stereoscopic 30° color fundus film photographs were taken of each eye. Photographs were centered on the optic disk and macula, and these photographs were converted to digital images using a high resolution scanner (Nikon LS2000; Nikon Inc., Tokyo, Japan).^{33,38}

Retinopathy severity

Our primary outcomes were prevalent retinopathy and change over time in retinopathy severity. Both eyes of participants in the MESA were graded for signs of retinopathy. Retinopathy lesions were classified using the modified Airlie House classification, as previously done in the Early Treatment Diabetic Retinopathy Study (ETDRS).³⁹ Lesions included intraretinal microvascular abnormalities, retinal vessel neovascularization, retinal microaneurysms, dot and blot hemorrhages, venous beading, cotton wool spots, and hard and soft exudates.⁴⁰ Our definition of retinopathy included those with mild non-proliferative retinopathy, moderate to severe non-proliferative retinopathy, and proliferative retinopathy. When grading of both eyes was available, the grade of the worse eye was used.

Similar methods were used to classify retinopathy in the BDES. Both eyes were graded for the presence of retinopathy lesions similar to the MESA, according to the modified Airlie House Classification.³⁴ A similar definition of retinopathy was used in the BDES.

Retinal vessel caliber measurements

Our secondary outcome was retinal venular diameter. In the MESA, investigators measured retinal microvascular caliber as per standard procedures using a computer-based program (IVAN, University of Wisconsin, Madison, WI, USA). Photographs centered on the optic disc, and graders measured all arterioles and venules passing through an area 0.5–1 disc diameter from the margin of the optic disc. These measurements were summarized as the central retinal venular and arteriolar equivalent (CRVE and CRAE), as described previously.^{37,41} For this analysis, only right eye measurements were used, as grading of the left eye differed between visit 2 and visit 5 in the MESA. Intra- and intergrader correlation coefficients ranged from 0.78 to 0.99.³⁷

In the BDES, trained graders measured the diameters of all venules and arterioles within an area measuring 0.5 to 1.0 of a disc diameter from the margin of the optic disc.³³ Standardized formulas were used to combine measurements of individual arterioles and venules into classification of CRAE and CRVE.⁴¹ Intergrader reliability was 0.79 and

intragrader reliability was 0.84.³³ For the current analyses, the right eye was analyzed, to match methods used in the MESA.

Covariates

Demographics, clinical history, physical examination, and laboratory testing were collected at baseline in the MESA. Diabetes mellitus was defined as a fasting plasma glucose level 126 mg/dl, or the use of any oral hypoglycemic medication or insulin. Serum creatinine was measured from baseline visit blood samples and estimated glomerular filtration rate (eGFR) was calculated utilizing the Chronic Kidney Disease Epidemiology Collaboration equation.^{31,42} Baseline serum intact parathyroid hormone (PTH) was measured using a 2-site immunoassay (Beckman-Coulter, Inc, Brea, USA) with an inter-assay coefficient of variation between 3.4 and 6.1%.⁴³ Serum fibroblast growth factor 23 (FGF23) was measured at baseline using the Kainos ELISA assay with coefficient of variations ranging from 6.7 to 12.4%.³⁵

Demographic, clinical history and blood samples were taken at baseline in the BDES. Investigators defined diabetes mellitus as either self-report with the use of insulin, any oral hypoglycemic medication, special diet or a glycosylated hemoglobin > 6.5%, or a glycosylated hemoglobin of 7.0% in absence of self-report. Serum creatinine was measured by an enzymatic method using the Roche Modular P Chemistry Analyzer (Roche Diagnostics). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.^{42,44} PTH and FGF23 were not measured in the BDES.

Statistical analysis

Multi-Ethnic Study of Atherosclerosis—We used standard descriptive statistics to compare demographic and clinical characteristics of the study populations according to phosphate quartiles. We used logistic regression to examine the odds of retinopathy prevalence according to serum phosphate, which was expressed as a continuous variable and in quartiles. We used linear regression to analyze the cross-sectional association of serum phosphate with CRAE and CRVE. In multivariable analyses for both outcomes in the MESA, we hierarchically adjusted for gender, other demographics (age, race/ethnicity), cardiovascular comorbidities (diabetes, systolic blood pressure, and eGFR) and other mineral metabolites (FGF23 and PTH). Given the strong links between diabetes and CKD with retinopathy,^{45,46} we conducted an a priori analysis that assessed whether the associations of serum phosphate with retinopathy presence and retinal vessel diameter in the fully adjusted model were modified by diabetes or eGFR by testing the significance of interaction terms. Due to effect modification by diabetes presence on the association of phosphate with prevalent retinopathy, we performed stratified analyses.

For prospective analyses, we used a similar hierarchical approach to multivariable modeling. We used logistic regression to investigate the association of serum phosphate with incident or change in retinopathy severity status. This was defined as a change from no retinopathy to any retinopathy or any increase in ETDRS severity category. We then conducted stratified analyses by diabetes status. Additionally, we used linear regression to investigate serum phosphate as a risk factor for change in CRVE and CRAE.

Beaver Dam Eye Study—We used similar analytic methods in the BDES to compare baseline characteristics of the study population according to phosphate quartiles. We tested the association between serum phosphate, expressed as a continuous variable and in quartiles, with prevalent retinopathy using logistic regression. We used a similar hierarchical modeling approach as for the analyses in the MESA. We used linear regression to analyze the cross-sectional crude- and adjusted-associations of serum phosphate with CRVE for our secondary outcome. We tested if our associations in the fully adjusted model were modified by diabetes status and eGFR. Similar to the MESA analyses, we conducted analyses stratified by diabetes due to observed effect modification by diabetes.

For our prospective analyses, we investigated crude and adjusted associations of serum phosphate with change in retinopathy using logistic regression and change in CRVE and CRAE over time using linear regression, similar to analyses completed in the MESA.

All analyses were performed using SAS version 9.4 (Cary, NC, USA). Any p -values < 0.05 were considered statistically significant for all analyses, including interactions terms.

Results

Multi-Ethnic Study of Atherosclerosis—primary outcome cross-sectional analyses

A total of 5837 participants had serum phosphate and retinopathy severity assessments. Mean age of the participant population was 61.8 (10.1) years, 52.7% of the population was female, 39.9% white, 26.6% Black, and 12.1% Asian. Mean eGFR was 78.4 (16.0) ml/min/1.73m², and mean serum phosphate was 3.66 (0.52) mg/dl. Overall, 11% of participants ($n = 637$) demonstrated retinopathy features at baseline. Clinical and demographic characteristics of the study participants according to phosphate quartiles are presented in Table 1.

In univariate analyses, baseline serum phosphate was not associated with the prevalent retinopathy (odds ratio [OR] per 1 mg/dl increase in serum phosphate, 1.08; 95% confidence interval [CI] 0.92–1.27; $p = 0.35$, Table 2). However, after adjustment for female gender, phosphate was significantly associated with prevalent retinopathy (OR per 1 mg/dl increase in serum phosphate, 1.19; 95% CI 1.00–1.41; $p = 0.049$, Table 2), demonstrating that female gender was a negative confounder. Female gender was associated with higher serum phosphate and with lower prevalence of retinopathy, as has been reported previously.^{47–49} The point estimate for the association of serum phosphate and retinopathy prevalence remained significant and was relatively unchanged after adjustment for all other covariates in the final model which included gender, age, race/ethnicity, diabetes, systolic blood pressure, eGFR, PTH, and FGF23 (Table 2). In quartile analyses, Quartile 4 versus Quartile 1 was significantly associated with a greater odds of retinopathy through Model 3. After adjustment for PTH and FGF23 in Model 4, this association was no longer significant. Neither PTH nor FGF23 were independently associated with retinopathy prevalence after adjustments for covariates.

Multi-Ethnic Study of Atherosclerosis—primary outcome stratified by diabetes

Whereas eGFR did not modify the relationship of serum phosphate with retinopathy severity (p for interaction = 0.53), we found a significant interaction between diabetes and serum

phosphate (p for interaction = 0.0006). In individuals with diabetes ($n = 732$), higher serum phosphate was independently associated with presence of retinopathy with a greater OR than in the entire study population (OR per 1 mg/dl increase in serum phosphate, 1.81; 95% CI 1.30–2.53; $p = 0.001$, Table 2). When phosphate was expressed in quartiles, participants in Quartile 4 versus Quartile 1 had a 1.90-fold greater odds of retinopathy (Table 2). Conversely, no association of serum phosphate with retinopathy was observed in those without diabetes.

Multi-Ethnic Study of Atherosclerosis—primary outcome prospective analyses

A total of 3919 of 5837 individuals had repeated fundus examination 8 years after the baseline exam at visit 5 and were included in our prospective analyses. Altogether, 305 individuals had developed incident retinopathy or had progression of their retinopathy severity between these visits. Phosphate was not significantly associated with incident or worsening retinopathy in the overall population (OR per 1 mg/dl increase in serum phosphate, 1.14; CI 0.88–1.47) or in analyses stratified by diabetes (Supplemental Table 1—online only).

Beaver Dam Eye Study—primary outcome cross-sectional analyses

A total of 4784 individuals had available serum phosphate and fundus examinations to investigate the presence of retinopathy at baseline. Clinical and demographic characteristics of study participants according to phosphate quartiles are presented in Table 1. Mean age was 61.9 (11.1), and 55.9% of the population was female. This cohort was predominantly white (<1% non-white). Mean serum phosphate was 3.77 (0.55) mg/dl and mean eGFR was 79.7 (18.0) ml/min/1.73m². Retinopathy prevalence was 10.5% ($n = 501$) at baseline. Similar to our findings in the MESA, serum phosphate in the univariate analyses was not associated with the presence of retinopathy. However, in the multivariable analyses that adjusted for age, gender, systolic blood pressure, diabetes and eGFR, serum phosphate was independently and significantly associated with prevalent retinopathy (OR per 1 unit increase in serum phosphate, 1.06; 95% CI 1.01–1.11; $p = 0.010$). In quartile analyses, Quartile 4 versus Quartile 1 was significantly associated with a greater odds of retinopathy (Quartile 4 versus Quartile 1 OR 1.35; 95% CI 1.00–1.82; $p = 0.033$; Table 3).

Beaver Dam Eye Study—primary outcome stratified by diabetes

As in the MESA, we found no effect modification by eGFR (p for interaction 0.08), but a significant interaction between diabetes and serum phosphate (p for interaction = 0.01) for the prevalent retinopathy outcome. In participants with diabetes ($n = 421$), higher serum phosphate was significantly associated with diabetic retinopathy with a greater OR compared to the whole population (OR per 1 mg/dl increase in serum phosphate, 1.16; 95% CI 1.05–1.29; $p = 0.03$; Table 3). Quartile analyses demonstrated that participants in Quartile 4 versus Quartile 1 had a 1.95-fold greater odds of retinopathy (Table 3). Conversely, no association was observed in those without diabetes, similar to results from the MESA.

Beaver Dam Eye Study—primary outcome prospective analyses

In the prospective analyses investigating changes in retinopathy over time, we included 3544 participants with baseline serum phosphate and year 5 fundus examinations available for grading. In multivariable adjusted models, serum phosphate was not significantly associated with incident retinopathy or change in retinopathy severity (OR per 1 mg/dl increase in serum phosphate, 0.99; CI 0.89–1.09; Supplemental Table 2—online only).

Multi-Ethnic Study of Atherosclerosis—secondary outcomes

A total of 3851 individuals had available measurements for retinal venular caliber and serum phosphate at baseline in the MESA. Higher serum phosphate was not significantly associated with baseline CRVE in univariate or multivariable modeling (Supplemental Table 3—online only). Overall, 2507 of 3851 individuals had repeated measurements of retinal venular caliber at visit 5 with a mean change in CRVE of 7.6 (13.1) μm . Concordant with our cross-sectional results, baseline serum phosphate was not significantly associated with change in retinal venous caliber over time either in the univariate or multivariable analyses (Supplemental Table 3). Serum phosphate was not associated with any arterial diameter measurement in cross-sectional or longitudinal analyses (data not shown).

Beaver Dam Eye Study—secondary outcomes

While vessel measurement was done for both eyes, we only used the right eye for our retinal vessel caliber analyses for consistency with the MESA data. Overall, 4686 individuals had measurements of retinal venular diameter in the right eye and serum phosphate measurements. Higher serum phosphate was not significantly associated with baseline retinal vein diameter in the univariate or multivariate analyses (Supplemental Table 4—online only). For our prospective analyses, we included 3393 participants with retinal vessel caliber measurements completed at exam 2. Serum phosphate was not significantly associated with change in retinal venular caliber over time (Supplemental Table 4) or with any retinal arterial diameter outcome (data not shown).

Discussion

We investigated the association of serum phosphate with retinal microvascular disease in individuals within two large community-based cohorts, the vast majority of whom had levels within the normal range of 2.5–4.5 mg/dl. Higher serum phosphate, even when within this range, was associated with greater odds of prevalent retinopathy in cross-sectional analyses in both the MESA and BDES. In stratified analyses, this effect was stronger and only appreciated in diabetic individuals. These results suggest that elevated serum phosphate is associated with deleterious effects on the microvasculature in the milieu of chronic disease states, particularly in individuals with diabetes.

We previously showed that higher serum phosphate concentrations were independently associated with retinopathy severity in patients with CKD (adjusted OR of being in one higher category of retinopathy severity: 1.19 per 1 SD increase in phosphate; 95% CI 1.05, 1.36).¹⁴ In the current study, we now demonstrate that elevated serum phosphate is independently associated with prevalent retinopathy in the MESA and BDES in diabetic

individuals, in whom serum phosphate levels in the highest compared to the lowest quartile are associated with nearly a 2-fold greater odds of retinopathy (MESA OR 1.90 Quartile 4 versus Quartile 1; BDES OR 1.95 Quartile 4 versus Quartile 1). Despite differences in population characteristics and methodology, the findings from all three studies are consistent. This lends support to the emerging hypothesis that an elevated level of serum phosphate is associated with microvascular disease, especially in populations with CKD and diabetes.

We postulate that elevated phosphate may have direct toxic effects on the endothelial vasculature which promote retinopathy.¹⁴ Along with data to suggest that phosphate induces vascular calcification, higher levels of serum phosphate are also linked to endothelial dysfunction.^{50–52} Although the underlying biology is unclear, we speculate that the resultant capillary leak and ischemia from endothelial dysfunction in already diseased states could contribute to the vascular changes of retinopathy.^{14,53}

Our prospective analyses did not show a similar association of serum phosphate with the development of incident retinopathy or change in retinopathy severity in either cohort. Prior data from prospective analyses in the MESA on macular degeneration demonstrate that those participants who returned for their visit 5 follow-up examination may have been younger and healthier.³² Loss of sicker participants and smaller study populations at follow-up may have hindered our ability to detect an effect of phosphate on retinopathy changes in our prospective analyses. On the other hand, this may represent that phosphate, although associated with retinopathy at baseline, does not directly induce retinopathy changes.

Higher serum phosphate concentrations were not associated with retinal venular caliber in either population-based cohort. Measurement of retinal vascular caliber in various pathologic disease states yields differing results. For example, diabetes, obesity and inflammatory disease states are associated with widening of retinal veins, but hypertension, CKD and aging result in narrowing of veins.^{14,23,33,54} We did not see a large change in retinal venular diameter between our study visits, and whether this is due to accuracy of measurements, lack of distensibility of veins, or other unmeasured confounders resulting in opposing changes is unknown.

Although we conducted our analyses in two large community-based cohorts with detailed covariate data and adjudication of retinal outcomes at baseline and in repeated assessments, we acknowledge additional limitations. Observational studies such as these cannot prove causality. Both cohorts had only single measurements of serum phosphate, non-fasting blood samples were collected in the BDES, and ophthalmologic examinations were taken at visit 2 in the MESA and not at the exact time of serum phosphate measurements. Given that the BDES was primarily of European ancestry and both cohorts have a low prevalence of CKD, the results may not be generalizable to all populations. Additionally, retinopathy grading at a single time point is subject to biologic variability. However, in cross-sectional analyses within MESA that excluded individuals whose retinal examinations improved over time, our primary results remain unchanged.

In two large community-based studies, serum phosphate, even when within the normal range, was associated with greater odds of retinopathy in diabetic participants, consistent with our findings in chronic kidney disease. Retinal vascular disease is a serious vision-threatening manifestation of chronic vascular disease with meaningful consequences for patients. Therapies designed to lower serum phosphate are frequently utilized in patients with CKD.⁵⁵ Identifying non-traditional and modifiable risk factors such as serum phosphate remains important for treatment and possibly for prevention of systemic microvascular disease in individuals with and without CKD. Although higher serum phosphate was not a risk factor for incident retinal disease in these populations, further longitudinal assessments with greater numbers of patients with diabetes and CKD may yield different results and necessitate further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of the MESA and BDES participants according to serum phosphate quartiles.

Multi-Ethnic Study of Atherosclerosis						
	Total N = 5837	Phosphate Q1 3.3 mg/dl N = 1639	Phosphate Q2 3.4-3.7 mg/dl N = 1232	Phosphate Q3 3.8-4.0 mg/dl N = 1684	Phosphate Q4 > 4.0 mg/dl N = 1282	P-value
Age, years	61.8 (10.1)	62.1 (10.1)	61.4 (10.1)	61.9 (10.1)	61.4 (10.0)	0.12
Sex, % female	52.7	30.1	45.7	60.7	77.9	<0.0001
Race/Ethnicity, %						
White Caucasian	39.9	40.1	37.1	41.6	40.3	0.20
Chinese American	12.1	11.4	12.3	11.3	13.6	
Black	26.6	27.2	28.8	25.5	24.9	
Hispanic	21.5	21.3	21.8	21.6	21.3	
Systolic BP, mm Hg	125.8 (21.1)	127.1 (20.5)	127.2 (21.1)	125.0 (21.4)	123.9 (21.3)	<0.0001
Diabetes mellitus, %	12.5	12.8	12.3	12.2	13.0	0.92
eGFR, ml/min/1.73m ²	78.4 (16.0)	78.4 (16.0)	80.0 (15.3)	78.0 (15.8)	77.4 (16.8)	0.0003
PTH, pg/ml	40.3 (31.1, 53.0)	44.2 (34.3, 58.5)	41.8 (32.8, 54.7)	39.0 (30.0, 50.9)	35.6 (27.9, 46.6)	<0.0001
FGF23, pg/ml	37.6 (30.4, 46.4)	36.5 (29.8, 45.1)	36.8 (29.7, 44.9)	38.3 (30.7, 47.1)	39.1 (31.7, 49.1)	<0.0001

Beaver Dam Eye Study						
	Total N = 4790	Phosphate Q1 3.3 mg/dl N = 1038	Phosphate Q2 3.4-3.7 mg/dl N = 1306	Phosphate Q3 3.8-4.1 mg/dl N = 1377	Phosphate Q4 > 4.1 mg/dl N = 1069	P-value
Age, years	61.9 (11.1)	62.6 (11.1)	62.9 (11.1)	61.9 (11.0)	60.1 (11.1)	<0.0001
Sex, % female	55.9	40.3	52.9	63.6	64.6	<0.0001
Systolic BP, mm Hg	132.1 (20.4)	136.1 (21.0)	133.3 (20.4)	130.8 (20.4)	128.6 (19.1)	<0.0001
Diabetes mellitus, %	8.8	9.4	10.0	7.8	8.0	0.1354
eGFR, ml/min/1.73m ²	79.7 (18.0)	80.9 (17.2)	79.4 (17.3)	79.5 (17.6)	78.9 (19.7)	0.0791

MESA, Multi-Ethnic Study of Atherosclerosis; BDES, Beaver Dam Eye Study; Q, quartile; N, number; BP, blood pressure; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; FGF23, fibroblast growth factor 23.

Table 2

Cross-sectional associations of serum phosphate concentration with retinopathy in the MESA.

Study population, N = 5837											
Per 1 mg/dl of serum phosphate			Quartile analyses								
OR	95% CI	p	Q1 (N = 1639)	Q2 (N = 1232)	Q3 (N = 1684)	Q4 (N = 1282)					
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	p for trend
Unadjusted	1.08	0.92, 1.27	0.35	Reference	0.98	0.77, 1.25	1.00	0.80, 1.25	1.10	0.87, 1.39	0.446
Model 1	1.19	1.00, 1.41	0.049	Reference	1.02	0.80, 1.30	1.09	0.87, 1.36	1.25	0.98, 1.60	0.079
Model 2	1.21	1.02, 1.43	0.03	Reference	1.02	0.80, 1.30	1.10	0.88, 1.39	1.28	1.00, 1.64	0.051
Model 3	1.24	1.03, 1.48	0.02	Reference	1.02	0.79, 1.32	1.14	0.90, 1.44	1.31	1.01, 1.69	0.037
Model 4	1.22	1.02, 1.47	0.03	Reference	1.02	0.79, 1.32	1.13	0.89, 1.44	1.29	0.98, 1.68	0.058
With diabetes, N = 732											
Per 1 mg/dl of serum phosphate			Quartile analyses								
OR	95% CI	p	Q1 (N = 209)	Q2 (N = 151)	Q3 (N = 206)	Q4 (N = 166)					
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	p for trend
Unadjusted	1.63	1.22, 2.17	0.001	Reference	0.93	0.59, 1.47	1.02	0.67, 1.55	1.74	1.13, 2.66	0.017
Model 1	1.73	1.27, 2.36	<0.001	Reference	0.96	0.60, 1.52	1.06	0.69, 1.62	1.85	1.18, 2.92	0.013
Model 2	1.78	1.29, 2.43	<0.001	Reference	0.96	0.60, 1.53	1.07	0.70, 1.66	1.90	1.20, 3.00	0.010
Model 3	1.87	1.36, 2.58	<0.001	Reference	0.95	0.60, 1.52	1.12	0.72, 1.73	2.01	1.26, 3.21	0.005
Model 4	1.81	1.30, 2.53	<0.001	Reference	0.95	0.59, 1.52	1.09	0.70, 1.69	1.90	1.17, 3.07	0.014
Without diabetes, N = 5105											
Per 1 mg/dl of serum phosphate			Quartile analyses								
OR	95% CI	p	Q1 (N = 1430)	Q2 (N = 1081)	Q3 (N = 1478)	Q4 (N = 1116)					
			OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	p for trend
Unadjusted	0.89	0.73, 1.09	0.257	Reference	1.02	0.76, 1.36	1.01	0.77, 1.33	0.88	0.66, 1.19	0.494
Model 1	0.96	0.78, 1.20	0.736	Reference	1.05	0.79, 1.42	1.09	0.83, 1.44	0.99	0.72, 1.37	0.891
Model 2	0.96	0.77, 1.20	0.724	Reference	1.05	0.78, 1.41	1.09	0.83, 1.44	0.99	0.72, 1.37	0.897
Model 3	1.00	0.80, 1.25	0.996	Reference	1.05	0.78, 1.41	1.13	0.85, 1.49	1.04	0.76, 1.44	0.630

Study population, N = 5837											
Per 1 mg/dl of serum phosphate					Quartile analyses						
					Q1 (N = 1639)	Q2 (N = 1232)	Q3 (N = 1684)	Q4 (N = 1282)			
					OR	95% CI	p				
					OR	95% CI		OR	95% CI	p for trend	
Model 4	1.01	0.80, 1.26	0.964	Reference	1.05	0.78, 1.42	1.13	0.85, 1.51	1.05	0.76, 1.47	0.601

Model 1 adjusts for gender.

Model 2 adjusts for covariates in Model 1 plus age, Black, Hispanic, Asian.

Model 3 adjusts for covariates in Model 2 plus systolic blood pressure, diabetes, eGFR.

Model 4 adjusts for covariates in Model 3 plus FGF23 and PTH.

MESA, Multi-ethnic Study of Atherosclerosis; N, number; Q, quartile; OR, odds ratio; CI confidence interval; eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone.

Table 3

Cross-sectional associations of serum phosphate with retinopathy in the BDES.

Study population, <i>N</i> = 4784											
Per 1 mg/dl in serum phosphate				Quartile analyses							
OR	95% CI	<i>p</i>		Q1 (<i>N</i> = 1037)	Q2 (<i>N</i> = 1305)	Q3 (<i>N</i> = 1373)	Q4 (<i>N</i> = 1069)				
				OR	95% CI	OR	95% CI	OR	95% CI	<i>p</i> for trend	
Unadjusted	1.02	0.97, 1.06	0.477	Reference	0.93	0.71, 1.21	0.90	0.69, 1.71	1.02	0.78, 1.35	0.932
Model 1	1.02	0.98, 1.07	0.268	Reference	0.95	0.73, 1.24	0.95	0.72, 1.23	1.08	0.82, 1.42	0.618
Model 2	1.04	1.00, 1.09	0.065	Reference	0.95	0.73, 1.24	0.98	0.75, 1.28	1.18	0.89, 1.57	0.238
Model 3	1.06	1.01, 1.11	0.010	Reference	0.99	0.75, 1.32	1.12	0.84, 1.49	1.35	1.00, 1.82	0.033

With diabetes, <i>N</i> = 421											
Per 1 mg/dl in serum phosphate				Quartile analyses							
OR	95% CI	<i>p</i>		Q1 (<i>N</i> = 98)	Q2 (<i>N</i> = 131)	Q3 (<i>N</i> = 106)	Q4 (<i>N</i> = 86)				
					OR	95% CI	OR	95% CI	OR	95% CI	<i>p</i> for trend
Unadjusted	1.14	1.05, 1.25	0.003	Reference	0.65	0.37, 1.13	1.04	0.59, 1.83	1.81	1.00, 3.26	0.016
Model 1	1.16	1.05, 1.27	0.002	Reference	0.67	0.38, 1.17	1.07	0.61, 1.90	1.90	1.04, 3.46	0.011
Model 2	1.16	1.06, 1.27	0.001	Reference	0.69	0.39, 1.21	1.09	0.62, 1.94	1.95	1.07, 3.57	0.009
Model 3	1.16	1.05, 1.29	0.003	Reference	0.74	0.42, 1.32	1.24	0.69, 2.23	1.95	1.03, 3.70	0.011

Without diabetes, <i>N</i> = 4363											
Per 1 mg/dl in serum phosphate				Quartile analyses							
OR	95% CI	<i>p</i>		Q1 (<i>N</i> = 939)	Q2 (<i>N</i> = 1174)	Q3 (<i>N</i> = 1267)	Q4 (<i>N</i> = 983)				
					OR	95% CI	OR	95% CI	OR	95% CI	<i>p</i> for trend
Unadjusted	0.99	0.94, 1.04	0.639	Reference	1.01	0.74, 1.38	0.92	0.67, 1.26	0.92	0.66, 1.29	0.514
Model 1	1.00	0.95, 1.05	0.940	Reference	1.04	0.76, 1.43	0.98	0.71, 1.35	0.98	0.70, 1.38	0.815
Model 2	1.01	0.96, 1.07	0.649	Reference	1.03	0.75, 1.41	1.01	0.73, 1.39	1.06	0.75, 1.49	0.793
Model 3	1.03	0.98, 1.08	0.279	Reference	1.08	0.78, 1.48	1.08	0.78, 1.48	1.18	0.84, 1.67	0.377

Model 1 adjusts for gender.

Model 2 adjusts for covariates in Model 1 plus age.

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Model 3 adjusts for covariates in Model 2 plus systolic blood pressure, diabetes, eGFR, BDES, Beaver Dam Eye Study; *N*, number; OR, odds ratio; Q, quartile, CI confidence interval; eGFR, estimated glomerular filtration rate.