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Original Investigation

Sex, Age, and the Association of Serum Phosphorus With All-Cause Mortality in Adults With Normal Kidney Function

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Background: High serum phosphorus levels are associated with cardiovascular morbidity and mortality in kidney disease. Although serum phosphorus levels possibly influence on mortality in individuals without kidney disease, this is uncertain because of the variable sex- and age-based distribution of serum phosphorus levels.

Study Design: Observational cohort study.

Setting & Participants: Clinical and biochemical data were collected from 138,735 adults undergoing routine health checkups in 3 tertiary hospitals. Individuals with estimated glomerular filtration rates < 60 mL/min/1.73 m^2 and urine dipstick albumin $\geq 1+$ were excluded.

Predictor: Sex-specific quartiles of serum phosphorus and sex.

Outcomes: All-cause mortality.

Results: The study included 92,756 individuals. Generally, women showed higher serum phosphorus levels than men. In women, serum phosphorus levels increased with age until 60 years old, then decreased with age. Men with higher serum phosphorus levels were younger and less likely to have hypertension, whereas women with higher serum phosphorus levels were older and more likely to have diabetes and hypertension. During a median follow-up of 75 months, 1,646 participants died. In the overall population, higher serum phosphorus levels were an independent predictor for all-cause mortality after adjustment (adjusted HR for the highest vs lowest quartile, 1.34; 95% CI, 1.15-1.56; $P < 0.001$). We observed that this increased risk was present in men but not in women (adjusted HR of 1.43 [95% CI, 1.22-1.68] vs 1.01 [95% CI, 0.76-1.33]), but interaction by sex was not significant ($P = 0.8$).

Limitations: A single phosphorus measurement and low power to test for interactions by sex and age.

Conclusions: We demonstrated that higher serum phosphorus levels influenced all-cause mortality in individuals with normal kidney function. Our findings suggest that the association may differ by sex, but future studies with adequate power to test for effect modification are needed to confirm our findings.

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INDEX WORDS: Serum phosphorus; hyperphosphatemia; risk factor; all-cause mortality; sex; age; normal kidney function.

Phosphorus is a vital mineral for several biological functions. Previous studies show that phosphorus consumption has increased steadily and now considerably exceeds the recommended dietary allowance.[1] In Korea, average phosphorus intake is ≥1,100 mg/d, which exceeds the Korean recommended dietary allowance of 700 mg/d, according to the 2012 Korean National Health and Nutrition Examination Survey (KNHANES). The prevalence of excessive phosphorus intake is second only to excessive sodium consumption in KNHANES.[2]

Excess phosphorus, especially a higher circulating serum phosphorus concentration, is a novel factor in adverse cardiovascular outcomes and mortality, mainly in patients with decreased kidney function.[3-5] The cardinal hypotheses linking higher phosphorus levels to cardiovascular outcomes are endothelial dysfunction,[6-8] vascular stiffness,[9,10] and vascular calcification.[11,12] Some studies failed to show a significant association between serum phosphorus level and mortality in patients with chronic kidney disease (CKD).[13,14] This heterogeneity is also found in the general population in individuals without evidence of kidney disease. Several epidemiologic studies have shown that higher serum phosphorus levels are associated with cardiovascular events,[15,16] incident heart failure,[17] and coronary artery disease.[12,18] However, reports investigating the association of serum phosphorus level with cardiovascular outcome or mortality have shown variable results in individuals with normal

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kidney function.[16,19-25] A possible explanation for this variability is the different distribution of serum phosphorus levels according to age,[26] sex,[20,26,27] hormonal status,[27,28] circadian variation,[29,30] and dietary phosphorus intake. Although a recent study regarding the interaction of dietary intake and diurnal variation demonstrated that fasting serum phosphorus levels are associated with all-cause mortality,[31] the study population included individuals with and without kidney disease. Another study showed sex heterogeneity in the association of serum phosphorus level and mortality in normal kidney function; however, because urinalysis results were unavailable, participants with CKD stage 1 or 2 would doubtless have been included. Furthermore, the effect of age was not considered.[20]

To elucidate the long-term clinical implications of serum phosphorus level as a risk factor for mortality in the general population without kidney disease, we investigated the association between serum phosphorus levels and all-cause mortality within a large adult cohort, focusing on the effect of age and sex.

METHODS

Study Population

This study cohort included individuals undergoing voluntary routine health checkups in 3 tertiary hospitals. Participants underwent checkups at the Seoul National University Hospital in 1995 to 2006 and at the Seoul National University Bundang Hospital and Health-care System Gangnam center in 2003 to 2009. These 3 hospitals share similar health care protocols. Because individuals requiring medical service tend to use tertiary hospitals, this sample is likely representative of individuals from various regions. When individuals had multiple visit data, we included only the data acquired in the first visit. Of 138,735 individuals, we included 92,756 who were aged 40 to 79 years. We excluded individuals with possible CKD, such as those with estimated glomerular filtration rates (eGFRs) < 60 mL/min/1.73 m^2 as calculated by the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation (n = 4,287), and evidence of albuminuria, indicated by urine dipstick albumin $\geq 1+$ (n = 14,823). We also excluded individuals who underwent colonoscopic examination on the same day, considering the possibility of electrolyte imbalance during bowel preparation (n = 1,900). Finally, we excluded individuals with advanced age (≥80 years; n = 24,969; Fig 1). The present study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board at Seoul National University Hospital (no. 1411-081-627).

Variable Measurements

Participants arrived at the hospital after an overnight fast for at least 12 hours. They participated in detailed in-person interviews, standardized physical examinations, and anthropometric measurements. Information about various comorbid conditions, including hypertension, diabetes mellitus, angina pectoris, cerebrovascular disease, and malignancy, were collected. Current smokers were those who were habitual smokers at the time of the interview. We measured blood pressure (BP) manually with a standardized sphygmomanometer after the participant had a minimum 5-minute rest while sitting in a chair. We recorded an average of 3 measurements for BP values. We calculated body mass index (BMI) using weight and height [weight (kg)/height (m^2)].

In addition, measurement of serum phosphorus, creatinine, albumin, lipid profiles, and other biochemical data was performed. To assess kidney function, we measured serum creatinine using the alkaline picrate Jaffé kinetic method by a Hitachi 7600 analyzer (Toshiba; 200FR); the same method was used at all hospitals. Serum creatinine levels were recalibrated with isotope-dilution mass spectrometry. As recommended by the College of American Pathologists (http://www.cap.org), recalibrated serum creatinine levels were calculated by taking measured serum creatinine (in mg/dL), raising to the power of -0.2418, and multiplying by 1.0734. We assessed kidney function using eGFR calculated by the CKD-EPI creatinine equation.[32] A single voided urine sample was collected

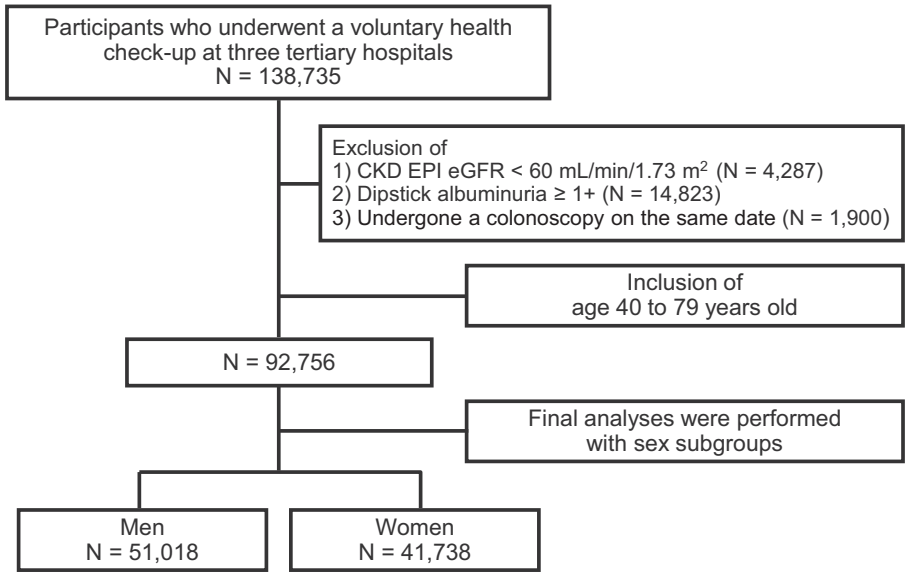

Figure 1. Study flow chart. Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.