Serum phosphorus as a predictor of low-grade albuminuria in a general population without evidence of chronic kidney disease

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Abstract

Background. High levels of serum phosphorus, even within the normal range, have been associated with cardiovascular (CV) morbidity. Low-grade albuminuria (LGA) was demonstrated to be related to increased CV events in various study populations. The present study aimed to investigate the association between serum phosphorus levels and LGA in the general population.

Methods. We examined the individuals who had undergone health inspections. We evaluated the correlation between serum phosphorus and LGA in 8953 participants (mean age, 47.4 years) with estimated glomerular filtration rates (eGFRs) ≥60 mL/min/1.73m² and urinary albumin-to-creatinine ratios (UACRs) <30 mg/g. Participants who underwent a colonoscopy were excluded.

Results. The mean UACR was significantly higher in the uppermost quartile group of serum phosphorus concentrations than in other quartile groups. In the multivariate regression analysis, serum phosphorus remained an independent predictor of increased UACR ($B = 0.610$, $P < 0.001$). Subgroup analyses showed that this association was maintained irrespective of age, gender, presence of hypertension or diabetes, body mass index and eGFR.

Conclusions. In our population-based study, higher serum phosphorus was independently related to LGA in individuals without evidence of renal dysfunction. Further investigations are warranted to clarify the precise mechanism of the association between serum phosphorus and LGA.

Keywords: serum phosphorus concentration; low-grade albuminuria; general population
Introduction

Elevated serum phosphorus concentrations have been found to be associated with adverse cardiovascular (CV) outcomes, mainly in subjects with impaired renal function [1–3]. The cardinal hypothesis linking elevated phosphorus levels to CV outcomes is vascular calcification, which stiffens arteries and leads to CV events [4]. Interestingly, recent observational studies have demonstrated that the association between serum phosphorus concentrations and CV morbidity or mortality exists in people without overt kidney disease [5] and even in the general healthy population [6]. In addition, several studies have established the association between phosphorus levels and surrogate markers of atherosclerosis such as carotid intima–media thickness [7] or coronary artery calcium levels [8] in the general population.

However, the underlying mechanisms linking excess serum phosphorus to CV disease in patients with normal renal function are not well understood. Although previous researches have suggested that subclinical renal dysfunction or secondary hyperparathyroidism could be regarded as possible causes [9, 10], such mechanisms are not likely to explain the relation between serum phosphorus and CV risk in the general population with normal renal function. Moreover, not all studies consistently demonstrate the association of serum phosphorus level with CV risks. For example, the CARDIA (Coronary Artery Risk Development in Young Adults) study suggested that higher phosphorus levels were associated with both protective and hazardous factors for CV diseases [8]. The Third National Health and Nutritional Examination Survey (NHANES III), which had a nationally representative cohort, also failed to show a correlation between serum phosphorus concentration and dietary phosphorus intake or traditional CV risk factors [11]. Therefore, further studies are required to determine the role of serum phosphorus in CV risk.

Although it has been reported that higher levels of albumin excretion [microalbuminuria; urinary albumin-to-creatinine ratio (UACR) 30–300 mg/g] had a close association with CV disease [12–16], a continuous association between elevated UACR and CV events has also been investigated at UACR levels below the microalbuminuria range. The first analysis of this association showed that CV risk increased almost 10-fold when the UACR rose from 10 to 30 mg/day in diabetes patients [17]. Data from the PREVEND (Prevention of Renal and Vascular End Stage Disease) study [18], HOPE (Heart Outcomes Prevention Evaluation) substudies [16], Copenhagen Heart Study [19], HUNT (The Nord-Trondelag Health Study) [20, 21] and the EPIC-Norfolk (European Prospective Investigation of Cancer) study [22] also demonstrated a positive dose-dependent relationship between urinary albumin excretion and cardiac morbidity or mortality. Moreover, it was suggested that such a relationship might begin at or even below UACR levels of 4–15 mg/g in various populations. Finally, recent studies have established that low-grade albuminuria (LGA), defined as below the threshold of microalbuminuria, is related to CV morbidity and mortality in the general population [23, 24]. The pathophysiological process of albuminuria is widely disputed. However, it is believed to mirror systemic endothelial dysfunction and thus albuminuria could be a surrogate marker or a condition that directly causes CV and/or renal risk [25, 26].

The association between phosphorus and LGA has not been reported in general population, despite both of them have been noticed as novel risk factors for CV morbidity and mortality in the general population. The present study thus explores the relationship between serum phosphorus concentrations and LGA in the general population among individuals free of kidney disease.

Materials and methods

Study subjects

From October 2003 to February 2009, a total of 14,095 adult participants (≥18 years old) completed a voluntary routine health checkup at Seoul National University Bundang Hospital. We analyzed data acquired during the first visit if a subject had multiple examinations. From these subjects, we excluded individuals with evidence of chronic kidney disease (CKD), such as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m² (n = 647), microalbuminuria (n = 802) or macroalbuminuria (n = 88), microscopic hematuria (n = 1656) and self-reported history of renal disease (n = 23). Participants who had undergone colonoscopic examination were also excluded due to the possibility of electrolyte imbalance and induction of albuminuria during bowel preparation (n = 2490). After exclusions, a total of 8953 individuals were eligible for the present cross-sectional investigation (Figure 1). This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board of the Seoul National University Bundang Hospital, Seongnam (H-1003-095-104).

Measurements

The subjects arrived at the hospital after an overnight fast of at least 12 h. They participated in detailed in-person interviews, standardized physical examinations, anthropometric measures and blood samples for biochemical analysis. Information about various comorbidities, including hypertension, diabetes mellitus, angina pectoris, acute myocardial infarction, cerebrovascular accident and malignancy was collected. The subjects answered questions about smoking status, exercise habits and use of non-prescription medications prior to the examination. Current smokers were defined as those who were habitual smokers at the time of the interview. Blood pressure was measured manually using a
standardized sphygmomanometer after a minimum of 5 min of rest while sitting in a chair; the average of three measurements was recorded. Body mass index (BMI) was calculated based on weight and height [weight (kg)/height (m^2)]. Waist circumference was measured at the level of the umbilicus by a single examiner, with the patient in a standing position. Measurement of serum phosphorus, creatinine, lipid profiles and other biochemicals was performed using the TBA-200FR (Toshiba, Tokyo, Japan). The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease equation [27]. A single morning void urine sample at the baseline examination was used to measure UACR. The urine sample was obtained after at least 12 h of fasting. The urinary albumin concentration was determined by a turbidometric immunossay (Dimension® Xpand® Plus Integrated Chemistry System, Siemens, Germany). LGA was defined as a UACR of <30 mg/g.

Hypertension was identified in individuals who met at least one of the following three criteria: physician’s diagnosis of hypertension, self-report of anti-hypertensive drug intake and systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg. Diabetes was diagnosed in subjects with a fasting serum glucose ≥126 mg/dL and in those who were identified during the health interview survey as actively using an oral hypoglycemic agent or insulin. Diagnosis of metabolic syndrome was based on the presence of three or more of the following: (i) waist circumference ≥90 cm for men or ≥80 cm for women [28], (ii) triglyceride levels ≥150 mg/dL, (iii) high-density lipoprotein (HDL) cholesterol levels <40 mg/dL for men or <50 mg/dL for women, (iv) SBP ≥130 mmHg or DBP ≥85 mmHg or the self-report of anti-hypertensive drug therapy and (v) fasting serum glucose level ≥100 mg/dL or the subject’s report of ongoing treatment with an oral hypoglycemic agent or insulin. A history of coronary artery disease was defined as a self-reported history of angina or acute myocardial infarction. Information regarding cerebrovascular accident and malignancy was acquired from self-reported histories.

Statistical analyses

Data are presented as frequencies and percentages for categorical variables. Continuous variables are reported as mean with standard deviation (SD). Serum phosphorus levels were divided into quartiles to compare means of other clinical variables, including UACR. Differences in the demographic factors and underlying comorbidities across the phosphorus groups were compared using the χ² test for trend (linear-by-linear association). Similarly, the one-way analysis of variance test was applied to demonstrate linearity of continuous variables across the phosphorus groups.

To assess the relationship between UACR and demographic and clinical data, univariate and multivariate linear regression analyses were performed. Variables that showed a significant association (P < 0.10) in the univariate analysis [age, underlying hypertension, coronary disease and hyperlipidemia, exercise, smoking habits, pulse pressure, pulse pressure, pulse pressure, pulse pressure, pulse pressure, pulse pressure, serum phosphorus, sodium, potassium, HDL cholesterol, triglyceride, total bilirubin, total protein and erythrocyte sedimentation rate (ESR)] or were of considerable theoretical relevance (sex and c-reactive protein) were included as candidate determinants of increased UACR. Covariates that were proven to have collinearity were excluded in multivariate analyses. Analysis of covariance with the Bonferroni correction was used to estimate adjusted distributions of UACR with respect to serum phosphorus levels. All analyses were conducted using the SPSS software (SPSS version 19.0, Chicago, IL), and P < 0.05 was considered statistically significant.

Results

Study population characteristics with respect to serum phosphorus concentration

A total of 8953 participants were included for final analyses. The mean age of the study subjects was 47.4 (11.7) years [mean (SD)]; 60.5% of the subjects were male. The mean concentration of phosphorus was 3.82 (0.90) mg/dL, and the mean UACR was 7.91 (5.35) mg/g. The demographic and clinical characteristics of the participants stratified by quartile values for serum phosphorus concentration are shown in Table 1. Distributions of comorbidities did not differ across the phosphorus quartiles, except for more frequent history of cerebrovascular accident and hyperlipidemia in the higher serum phosphorus groups. The proportion of participants who exercised regularly increased with increasing serum phosphorus concentration.

Subjects with higher serum phosphorus tended to have higher pulse pressure, lower DBP and lower eGFRs. The levels of serum calcium, potassium, HDL cholesterol, alkaline phosphatase, total bilirubin, total protein and ESRs were lower in the higher phosphorus groups. The level of serum sodium and albumin increased with increasing phosphorus across the groups. Alkaline phosphatase levels decreased in the upper two quartile serum phosphorus groups.

The mean UACR was significantly higher (up to 9.16 mg/g) in the uppermost quartile serum phosphorus group, compared with that of the lowest quartile serum phosphorus group (P < 0.001). On the other hand, mean UACR in the second and third quartile groups did not differ from those of the lowest quartile group. When the UACR was divided into quartiles, the higher serum phosphorus group included a significantly higher proportion of the uppermost UACR quartile (P < 0.001, Figure 2). Moreover, the distribution of UACRs assumed an ‘ascending stair’ pattern in the highest quartile group contrary to the ‘descending stair’ pattern seen in the first to third quartile phosphorus groups.

Predictors of LGA

Results of univariate and multivariate linear regression analyses of UACR associations are presented in Table 2. In unadjusted models, increased UACR was associated with younger age, underlying hypertension/ischemic heart disease/hyperlipidemia, regular exercise, current smoking habit, increased pulse pressure and increased serum phosphorus, sodium and triglyceride levels. Negative correlations with UACR were seen for renal function, serum calcium and potassium levels, HDL cholesterol levels, total bilirubin, total protein and ESR. After adjustment of all significant univariate factors, serum phosphorus levels were demonstrated to be a potent predictor of increased UACR [regression coefficient (B) = 0.610, P < 0.001]. High serum sodium, low serum potassium, increased pulse pressure, low total bilirubin and low total protein levels also remained significant determinants of increased UACR.

Figure 3 shows unadjusted and adjusted mean UACRs among the serum phosphorus quartile groups. Age- and sex-adjusted UACRs were positively related to serum phosphorus quartile groups, based on the P-value for the Bonferroni correction (P < 0.001). The mean UACR for the highest quartile serum phosphorus group was 9.14 mg/g [95% confidence interval (CI), 8.93–9.35; standard error of mean (SEM), 0.108] when adjusted for age and sex. The mean UACR in the highest serum phosphorus quartile was 9.00 mg/g (95% CI, 8.73–9.26; SEM 0.137) when all related covariates were adjusted.
When the study population was divided into two groups at a cutoff UACR of 9.00 mg/g, the mean value of serum phosphorus was 4.1 (1.1) mg/dL in subjects with a UACR above the cutoff point and 3.7 (0.8) mg/dL in those with a UACR below the cutoff point.

Subgroup analyses

To explore how the association of serum phosphorus with UACR differed with respect to subject characteristics, we performed subgroup analyses with respect to age (≥65 and <65 years), gender, presence or absence of diabetes mellitus or hypertension, BMI (<25 and ≥25 kg/m²) and eGFR level (≥90 and 60–90 mL/min/1.73m²). Such clinical variables were selected because they were considered to be associated with serum phosphorus concentrations. Table 3 shows the predictors of higher UACRs in each subgroup after multivariate linear regression analyses.

Higher serum phosphorus levels were significantly associated with increased urine albumin excretion consistently across age, sex, diabetes and hypertensive status and levels of BMI and eGFR after covariable adjustment. In contrast to serum phosphorus levels, other independent predictors of UACR, such as serum sodium, serum potassium and pulse pressure, remained significant only in selected subgroups. Serum potassium levels failed to show the inverse correlation with LGA in female subjects and in subjects with hypertension. Serum sodium levels lost significance as a predictor for UACR in female subjects, subjects ≥65 years old, the normotensive and diabetic subgroups, the subgroup with higher BMIs and the subgroup with higher eGFRs. Higher pulse pressure was associated with increased UACR in individuals <65 years of age and in those with an eGFR of 60–90 mL/min/1.73m².

For each of these subgroups, potential confounder-adjusted distributions of UACRs according to serum phosphorus quartile group are analyzed. UACRs were consistently higher from the highest serum phosphorus quartile group (≥4.1 mg/dL) compared to other
phosphorus groups in all the subgroups except in subjects with hypertension (P = 0.106, data not shown).

**Discussion**

The present study demonstrates that higher serum phosphorus levels, even within the normal range, are positively and independently associated with increased LGA, irrespective of age, BMI, renal function or the existence of diabetes or hypertension. To our knowledge, this investigation is the first to demonstrate the interesting relationship between serum phosphorus and LGA, both of which have been recently explored for their novel associations with CV diseases in the general population.

In our study, higher serum phosphorus concentration was a strong predictor of increased UACR in the general population, both continuously and categorically. The UACR value of 9.0 mg/g, determined to be the multivariate-adjusted mean in the highest quartile serum phosphorus group, is within the range of albuminuria that has been associated with increasing CV risk or mortality in previous studies [16, 20, 21, 24]. Moreover, the UACR cutoff point identified in our study was similar to that suggested in a previous study as the level above which CKD prevalence increases in subjects with metabolic syndrome [29]. These results support the notion that elevated serum phosphorus concentrations, >4.1 mg/dL in the present study, are associated with increasing LGA and consequently with CV disease.

The pathophysiological mechanism linking serum phosphorus concentration to LGA is not yet understood. Interestingly, however, it has been suggested that both serum phosphorus concentration [7, 30] and LGA [31, 32] predict the development and progression of atherosclerosis through deteriorating endothelial dysfunction. Shuto et al. [30] demonstrated that dietary phosphorus loading increased serum phosphorus levels and, while within normal range, decreased flow-mediated dilatation, a surrogate marker of endothelial function. In albuminuria, dysfunction of the glomerular endothelial cells may lead to increased albumin excretion [33]. Furthermore, flow-mediated dilatation was found to be inversely related to albumin excretion [34, 35]. In the present study, increased pulse pressure was another predictor of LGA even after multivariate adjustment. Elevation of pulse pressure was also found to be inversely correlated with endothelium-dependent...
vasodilatation in a previous study [36]. Taken together, both serum phosphorus and urinary albumin excretion may reflect systemic endothelial dysfunction, which in turn may be a precursor to atherosclerosis and CV morbidity and mortality.

The present study shows that serum sodium concentration increases, as does UACR, in the higher serum phosphorus group. Although the change is subtle (~1.2 mEq/L), recent studies suggest that such a small increase in serum sodium may affect blood pressure both directly and indirectly [37, 38]. The mechanisms focused on the tendency for an increase in extracellular fluid volume. However, a recent study suggested that the endothelial stiffness and deformability that were influenced imparted by small changes in serum sodium concentration indicates the involvement of a sodium-mediated function in blood vessels [39]. These data are in line with the results of our study, which show a relationship between LGA and higher serum sodium concentrations. An inverse relationship between serum potassium and UACR could also be supported by previous observations that dietary supplementation of potassium attenuated hypertension and increased vascular compliance by endothelial-dependent vasodilators, without significant structural differences in the endothelium [40–42].

The strengths of the present study include that it was intended for the large number of Asian individuals without evidence of renal disease. Moreover, other CV risk factors and laboratory findings were evaluated according to serum phosphorus concentrations. Also, it is important to point out that this observational study suggested the novel relationship between serum phosphorus concentration and LGA in terms of endothelial dysfunction. However, this study also has some limitations that should be considered. Firstly, the information about dietary phosphate was lacking in this analysis. Previous investigators have proven that dietary phosphorus loading might be a risk factor for CV disease by causing elevation of serum phosphorus levels and impairment of vasodilatation even in healthy people [30]. In contrast, another population-based study demonstrated that the magnitude of the association of dietary phosphorus intake with serum phosphorus concentrations remained biologically and clinically small [11]. Due to these uncertainties, the impact of dietary practices on serum phosphorus level in our population should have been explored in this study. Secondly, our data lacked information about parathyroid hormone, 1,25-dihydroxyvitamin D levels and fibroblast growth factor 23. Such hormones are known to regulate phosphorus homeostasis, and the kidney has a major role in this regulation. Although we intended to minimize the potential confounding influence of renal function by excluding individuals with impaired kidney function, renal disease history and microscopic hematuria and by

<table>
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<th>Adjusted $B^*$</th>
<th>95% CI</th>
<th>P</th>
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<td>Age</td>
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<td>≥65 years (821)</td>
<td>1.002</td>
<td>0.567 - 1.437</td>
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<tr>
<td>Gender</td>
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<td>0.468 - 1.181</td>
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<tr>
<td></td>
<td>Male (5421)</td>
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<td>0.358 - 0.792</td>
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<td>0.624</td>
<td>0.444 - 0.803</td>
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<td></td>
<td>Yes (616)</td>
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<td>Hypertension</td>
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<td></td>
<td>Yes (1492)</td>
<td>0.825</td>
<td>0.468 - 1.181</td>
</tr>
<tr>
<td>BMI</td>
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<td></td>
<td>≥25 kg/m² (2890)</td>
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<td>eGFR</td>
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<td>0.466 - 0.825</td>
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$B^*$, Regression coefficient with serum phosphorus levels.
performing subgroup analyses according to eGFR, there may have been further confounding influences that remained undetected. Thirdly, because our study was cross-sectional, we demonstrated only the association between serum phosphorus and LGA; a prospective study is needed to elucidate the relationship between these two factors and consequently to the hard outcome such as development of CV events. Fourthly, albuminuria was measured only once, and corrections were not made for potential variability in urine concentrations.

In conclusion, we demonstrated that serum phosphorus concentration was independently and significantly related to LGA, a novel surrogate marker for CV morbidity, in subjects with apparently normal renal function, irrespective of demographic or clinical background. Therefore, even if within the normal range, individuals with higher serum phosphorus levels (>4.1 mg/dL) should be cautiously monitored regarding their CV risk factors. Further prospective studies are now warranted to evaluate the clinical implications of our new findings.

Conflict of interest statement. None declared.

References


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Tonsillectomy has beneficial effects on remission and progression of IgA nephropathy independent of steroid therapy

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**Abstract**

**Background.** Indication of tonsillectomy in IgA nephropathy is controversial. The purpose of this study was to examine the efficacy of tonsillectomy on remission and progression of IgA nephropathy.

**Methods.** We conducted a single-center 7-year historical cohort study in 200 patients with biopsy-proven IgA nephropathy. Study outcomes were clinical remission defined as disappearance of urine abnormalities at two consecutive visits, glomerular filtration rate (GFR) decline defined as 30% GFR decrease from baseline and GFR slope during the follow-up.

**Results.** Seventy of the 200 patients received tonsillectomy. Tonsillectomy was associated with increased incidence of clinical remission (P = 0.01, log-rank test) and decreased incidence of GFR decline (P = 0.01, log-rank test). After adjustment for age and gender, hazard ratios in tonsillectomy were 3.90 (95% confidence interval 2.46–6.18) for clinical remission and 0.14 (0.02–1.03) for GFR decline. After further adjustment for laboratory (baseline mean arterial pressure, GFR, 24-h proteinuria and hematuria score), histological (mesangial score, segmental sclerosis or adhesion, endocapillary proliferation and interstitial fibrosis) or treatment variables (steroid and renin–angiotensin system inhibitors), similar results were obtained in each model. Even after exclusion of 69 steroid-treated patients, results did not change. GFR slopes in tonsillectomy and non-tonsillectomy groups were 0.60 ± 3.65 and −1.64 ± 2.59 mL/min/1.73 m²/year, respectively. In the multiple regression model, tonsillectomy prevented GFR decline during the follow-up period (regression coefficient 2.00, P = 0.01).

**Conclusion.** Tonsillectomy was associated with a favorable renal outcome of IgA nephropathy in terms of clinical remission and delayed renal deterioration even in non-steroid-treated patients.

**Keywords:** clinical remission; IgA nephropathy; renal deterioration; steroid therapy; tonsillectomy

**Introduction**

IgA nephropathy is the most common type of primary glomerulonephritis. Clinical course of this disease