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Outcomes associated to serum phosphate levels in patients with suspected acute coronary syndrome

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ABSTRACT

Background: We investigated the association between phosphate and the risk of adverse clinical outcomes in patients with manifest cardiovascular disease (CVD).
Methods: Observational study of patients hospitalized during 2006–2011 in Stockholm, Sweden, because of suspected acute coronary syndrome (ACS). The exposure was serum phosphate during the hospitalization. We modeled the association between phosphate and in-hospital death or in-hospital events (composite of myocardial infarction, cardiogenic shock, resuscitated cardiac arrest, atrial fibrillation, or atrioventricular block) as well as the one-year post-discharge risk of death or cardiovascular event (composite of myocardial re-infarction, heart failure and stroke). Confounders included demographics, comorbidities, kidney function, diagnoses, in-hospital procedures and therapies.
Results: Included were 2547 patients (68% men, mean age 67 ± 14 years) with median phosphate of 1.10 (range 0.14–4.20) mmol/L. During hospitalization, 198 patients died and 328 suffered an adverse event. Within one year post-discharge, further 381 deaths and 632 CVD events occurred. The associations of phosphate with mortality and CVD were J-shaped, with highest risk magnitudes at higher phosphate levels. For instance, compared to patients in the 50th percentile of phosphate distribution, those above the 75th percentile (1.3 mmol/L, normal range) had significantly higher odds for in-hospital death [odds ratio 1.36, 95% confidence interval (CI) (1.08–1.71)] and of CVD post-discharge [sub-hazard ratios 1.17 (1.03–1.33)].
Conclusions: In patients with suspected ACS, both higher and lower phosphate levels associated with increased risk of adverse outcomes during the index hospitalization and within one year post-discharge. The risk association was present already within normal-range serum phosphate values.

1. Introduction

Phosphate is an essential micronutrient being a structural component of nucleic acids, adenosine triphosphate, and membranes phospholipids. Phosphate also plays a critical role in cellular signaling, mineral metabolism and energy exchange. In humans, phosphate homeostasis is maintained by a delicate balance between intestinal absorption, renal excretion, as well as influx to and efflux from bone [1,2]. Due to the dependence of phosphate elimination by the kidneys, hyperphosphatemia is a common metabolic complication in patients with advanced chronic kidney disease (CKD) [1]. Mechanistic investigations have uncovered toxic effects of phosphate on vascular calcification, endothelial dysfunction, left ventricular hypertrophy and the aging process [1]. Observational studies throughout the spectrum of CKD support the concept of hyperphosphatemia as a risk factor for cardiovascular disease (CVD) and mortality [3–5]. Dietary and pharmacological management of serum phosphate is considered a cornerstone therapy in patients with advanced CKD to prevent these complications [6].

A better understanding of the possible harm associated with serum phosphate may be of particular relevance in patients with established

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CVD, given that the prevalence of CKD exceeds 1/3 in this patient population [7]. Moreover, it has been shown that excess phosphate increases the risk of death and CVD also in patients with normal kidney function [8–12]. In this study we assess the association between serum phosphate levels and short-term clinical outcomes in a large cohort of unselected patients admitted to hospital because of suspected acute coronary syndrome (ACS).

2. Methods

2.1. Study population

This study includes all citizens from the region of Stockholm, Sweden, hospitalized in cardiac care units (CCUs) between 2006 and 2011. The study population is the result of a linkage between the nationwide Swedish Web-System for Enhancement and Development of Evidence-Based care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry [13], and the Stockholm CREAtinine Measurements (SCREAM) project [14]. SWEDEHEART includes patients who are admitted to CCUs or other specialized facilities because of symptoms suggestive of ACS in Sweden. The registry prospectively collects information on patient demographics, cardiovascular risk factors, medical histories, and in-hospital medical treatments including coronary revascularization procedures, hospital outcomes, discharge medications, and diagnoses. SCREAM is a repository of laboratory analyses performed during 2006–2011 by the sole healthcare system of the region of Stockholm. The only inclusion criteria to enter SCREAM are to be residing in Stockholm and to undertake at least one creatinine test within a six year period. Because of the indications of creatinine testing in CVD and the fact that SWEDEHEART collects creatinine information at admission as per protocol, the coverage of CVD patients of the region was estimated in 98% [14]. Linkage between SWEDEHEART and SCREAM was possible through the personal identification number of each citizen. The study protocol was approved by the regional Ethics Committee in Stockholm.

Included in this study were all patients registered in SWEDEHEART within the region of Stockholm (n = 37,161) between January 1st 2006 and July 1st 2011. For this analysis, we include any patient undergoing at least one serum phosphate test within 24-h before hospital admission and the discharge date. A total of 2547 patients (1743 men and 804 women, mean age 67 ± 14 years) were identified and constitute the study population (Supplementary Fig. S1). Compared with non-included patients, included patients were more often men and had significantly higher proportion of comorbidities, lower kidney function, and higher number of in-hospital events (Supplement Table S1).

2.2. Serum phosphate and other laboratory data

All laboratory measurements were performed during the patient's CCUs admission and by the clinical laboratories providing services to Stockholm County Council. Serum phosphate levels were measured by spectrophotometry with ammonium molybdenum, with reference ranges between 0.8 and 1.5 mmol/L. The first available serum calcium and serum albumin tests during the hospitalization were extracted and used to calculate corrected serum calcium as follows = *observed serum calcium (mmol/L) + 0.02 * (40 g/L − patient albuminemia g/L)* [15]. Serum creatinine was measured using methods standardized to isotope dilution by mass spectrometry standards. Estimated glomerular filtration rate (eGFR) was calculated by the 2009 CKD-EPI equation, and eGFR strata categorized as: ≥60, 30–59, 15–29, and below 15 mL/min/1.73 m^2 or dialysis [16]. Dialysis patients were identified via linkage with the Swedish Renal Register (http://www.snronline.se).

2.3. Serum phosphate variability and selection of measurement

For the 2457 included patients, a total of 4475 serum phosphate measurements were ordered during the CCUs stay. Whereas most patients (74%) had only one measurement available, 13% had two measurements and the remaining 13% had three or more measurements during the whole CCUs stay. Serum phosphate levels tended to remain constant over time without much variability (Supplement Table S2, Supplement Fig. S2), we selected the first available serum phosphate measurement per patient as our main exposure.

2.4. Study outcomes

In-hospital outcomes considered death and a composite of in-hospital events (myocardial re-infarction, cardiogenic shock, resuscitated cardiac arrest, atrial fibrillation, or atrioventricular block) as per protocol registered in SWEDEHEART by the treating physician. One-year post-discharge outcomes were based on International Classification of Diseases (ICD)-10 codes and considered death and a composite of CVD events (myocardial re-infarction, heart failure, stroke up to 365 days post-discharge by ICD-10 codes (Supplement Item S1)). Deaths, causes of death and new CVD events were retrieved from linkages with the National Board of Health and Welfare's Cause-of-death and the Patient registers, which have a complete national coverage and no loss to follow-up.

2.5. Statistical analysis

Patient baseline characteristics stratified by quartile of phosphate distribution are described by using means and proportions. P-for trend analysis was used to assess linear trends across the quartiles. We imputed missing values of serum creatinine (missing in 62 patients, 2% of the sample), calcium (missing in 510 patients, 20% of the sample) and albumin (missing in 318 patients, 12% of the sample).

Odds ratios (OR) and 95% confidence interval (CI) were estimated using logistic regression models to determine the association between serum phosphate and in-hospital outcomes. We adjusted the multivariable models for age (per year), sex, eGFR (per mL/min/1.73 m^2), comorbidities (hypertension, diabetes, prior myocardial infarction, history of heart failure, prior stroke), main diagnoses (ACS, heart failure, arrhythmia, others), type of myocardial infarction [ST-elevation myocardial infarction (STEMI)/non-STEMI], and medication [angiotensin converting enzyme inhibiter/angiotensin receptor blocker (ACEI/ARB), dual antiplatelet therapy (DAPT), beta-blocker, and statins] on admission.

Hazard ratios (HR) and 95% CI were estimated using Cox–proportional hazard models to determine the association between serum phosphate and 1-year post-discharge outcomes. For the analysis of CVD outcomes, we performed Fine-Gray models taking death due to non-CVD causes as a competing event. Multivariable models were adjusted for age (per year), sex, eGFR (per mL/min/1.73m^2), comorbidities (hypertension, diabetes, prior myocardial infarction, history of heart failure, prior stroke), main diagnoses (ACS, heart failure, arrhythmia, others), type of myocardial infarction (STEMI and non-STEMI), in-hospital procedures [coronary angiography, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)], and medication (ACEI/ARB, DAPT, beta-blocker, and statins) at discharge.

We investigated "dose-response" relationships between serum phosphate and outcomes using restricted cubic splines. By using splines with knots at fixed percentiles of phosphate distribution (5th, 25th, 50th, 75th, and 95th percentiles), we adopted a procedure of tabular presentation of the phosphate-associated multivariable risk [17]. P value for nonlinearity was obtained by testing the coefficient of the second spline transformation equal to zero. Interaction terms in a priori specified strata were used to evaluate whether older age (≥65 vs <65 years), sex (women/men), eGFR strata (≥60, 30–59, 15–29, and <15 mL/min/1.73 m^2 or dialysis), and main diagnosis (ACS/non-ACS) modified the association between serum phosphate and the study outcomes. As sensitivity analysis, we tested if the associations observed were explained by accompanying serum calcium disturbances. To that end, we calculated restricted cubic splines associating serum calcium, and the product of calcium × phosphate, with the occurrence of in-hospital and one-year post-discharge outcomes. All statistical analyses were performed using STATA version 14.0 (Stata Corporation, College Station, TX, USA).

3. Results

A total of 2547 patients were included. Serum phosphate concentrations approximated to a normal distribution, with a mean level of 1.20 [standard deviation, (SD) 0.46] and a median of 1.10 (range from 0.14 to 4.20) mmol/L (supplement Fig. S2). There were 386 (15%) participants with hyperphosphatemia (>1.5 mmol/L), and 286 (11%) with hypophosphatemia (<0.8 mmol/L).

3.1. Baseline characteristics, in-hospital care and medication

Baseline characteristics, in-hospital care and medications are shown in Table 1. Age, the proportion of women, diabetics, hypertensives and previous CVD increased across higher phosphate quartiles. Kidney function and serum albumin decreased. As many as 67% of the admitted patients had confirmed ACS and their proportion tended to decrease with higher phosphate quartiles. The majority of ACS cases were non-STEMI. The number of patients with a history of heart failure or arrhythmia tended to increase with higher phosphate quartiles. In multivariable regression, age, eGFR, and serum calcium were inversely and independently associated with serum phosphate, whereas female gender appeared as a positive correlate (Supplement Table S3).

3.2. Serum phosphate levels and in-hospital adverse events

A total of 328 (13%) patients experienced in-hospital adverse events and 194 (8%) died during the hospitalization (Table 2). Spline curves showed a J-shaped relationship between serum phosphate and the odds of these outcomes. Both lower and higher phosphate values were associated with a higher risk (Fig. 1A). Table 3 shows crude and adjusted ORs for selected serum phosphate concentrations. For instance, as compared to serum phosphate concentration of 1.1 mmol/L (median value), a phosphate concentration of 1.3 mmol/L showed 69% higher unadjusted risk of death (OR 1.69, 95% CI 1.38–2.07), and 400% higher unadjusted mortality for 2.1 mmol/L of phosphate (OR 5.01, 95% CI 3.19–7.87). For the outcome of in-hospital events, we observed

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