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Review

Serum phosphorus, cardiovascular and all-cause mortality in the general population: A meta-analysis

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ABSTRACT

Background: The association between elevated serum phosphorus concentration and cardiovascular or all-cause mortality yielded conflicting results.
Objective: To assess the association between elevated serum phosphorus concentration and cardiovascular or all-cause mortality in the general population by conducting a meta-analysis.
Methods: We systematically searched the Pubmed and Embase databases until March 2016 for the prospective studies investigating serum phosphorus concentration and cardiovascular or all-cause mortality in the general population. We pooled risk ratio (RR) and corresponding 95% confidence intervals (CI) for the highest versus the reference category of serum concentration of phosphorus.
Results: Six prospective cohort studies involving 120,269 subjects were identified.
When compared the highest with the reference concentration of serum phosphorus, the pooled RR of cardiovascular mortality and all-cause mortality were 1.36 (95% CI 1.07–1.72) and 1.35 for all-cause mortality (95% CI 1.15–1.58), respectively. Stratified analyses revealed that elevated serum phosphorus significantly increased all-cause mortality risk among men (RR 1.33; 95% CI 1.11–1.60), but not in women (RR 1.09; 95% CI 0.89–1.33).
Conclusions: Elevated serum phosphorus concentration is independently associated with excessive risk of cardiovascular and all-cause mortality in the general population without chronic kidney disease. Serum phosphorus on all-cause mortality risk appears to be pronounced in men but exhibits no clear effect on women. However, gender difference of elevated serum phosphorus on mortality risk should be verified by more prospective studies.

Contents

1. Introduction

Phosphorus in the form of inorganic or organic phosphate is a vital mineral in the body. Phosphate plays an essential role in energy

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metabolism, bone mineralization and intracellular signaling. Phosphorus homeostasis is usually maintained by kidney and gastrointestinal tract [1]. Vitamin D, parathyroid hormone, and fibroblast growth factor-23 can regulate the phosphate balance [2,3]. Increased serum phosphorus concentration has been associated with impaired intestinal phosphate absorption, renal phosphate reabsorption or phosphate metabolism [4]. Particularly, decreased renal excretion is the most common cause of hyperphosphatemia [5].

A high-concentration of phosphorus has been proposed as a risk factor for cardiovascular diseases [6]. In patients with chronic kidney disease [7] and undergoing dialysis [8], hyperphosphatemia or elevated serum phosphorus concentration has been linked to an increased risk of cardiovascular and all-cause mortality. Several epidemiological studies have indicated that elevated serum phosphorus or phosphate concentration is associated with increased risk of cardiovascular and all-cause mortality in individuals with normal kidney function [9–15]. However, conflicting results [10,12,13,15] on the association have been reported in the general population. These inconsistent findings could be correlated to the population studied, with age or gender difference considered. Previously published meta-analysis [16] only analyzed the association in patients with chronic kidney disease and could not generalize to the general population.

We therefore conducted this meta-analysis on the basis of prospective observational studies to assess the association between elevated serum phosphorus concentration and cardiovascular and all-cause mortality risk in the general population.

2. Materials and methods

2.1. Search strategy

We performed this meta-analysis in accordance with the Meta-analysis of Observational Studies in Epidemiology reporting guidelines [17]. Two authors (J. Li and J. Liu) independently searched the PubMed, and Embase from their inception to March 2016. Keywords used for search included the following text words and Medical Subject Headings terms: “phosphate” OR “phosphorus” OR “hyperphosphatemia” AND “mortality” OR “death” AND “prospective studies” OR “longitudinal study” OR “follow-up”. Only articles published in English were included. We also manually searched the reference lists of the retrieved articles to identify any additional studies. If the outcome interesting was not reported, the corresponding author was contacted by e-mail for additional information.

2.2. Inclusion and exclusion criteria

Studies that fulfilled the following criteria were considered eligible: 1) prospective observational study; 2) subjects in the general population; 3) the exposure was circulating phosphorus or phosphate; 4) reported at least age-adjusted risk estimate of cardiovascular or all-cause mortality associated with the highest versus the reference category of serum phosphorus or phosphate concentration. When multiple publications from the same studied population, we only selected the article with the complete information. Studies were excluded: 1) participants suffered from dialysis/kidney disease; 2) participants from a high cardiovascular risk group; 3) not reporting risk estimate by the highest versus the reference phosphorus category; and 4) abstracts and unpublished studies.

2.3. Data extraction and quality assessment

Data extraction was undertaken independently by two authors (J. Li and J. Liu). The following information was also extracted: the first author's name, publication year, country, study design, number of participants, percentage of male gender, mean age or age range, baseline estimated glomerular filtration rate (eGFR), method of phosphorus assay, number of death events, most fully adjusted risk ratio (RR) and its 95% confidence interval (CI), follow-up duration, and adjustment for confounding factors. Newcastle-Ottawa Scale (NOS) of cohort studies was selected to assess methodological quality [18],including the domains of subject selection, comparability of groups, and ascertainment of outcomes. Studies achieving 6 stars or more were considered high-quality; whereas those with a rating of ≤5 stars were thought to be low-quality.

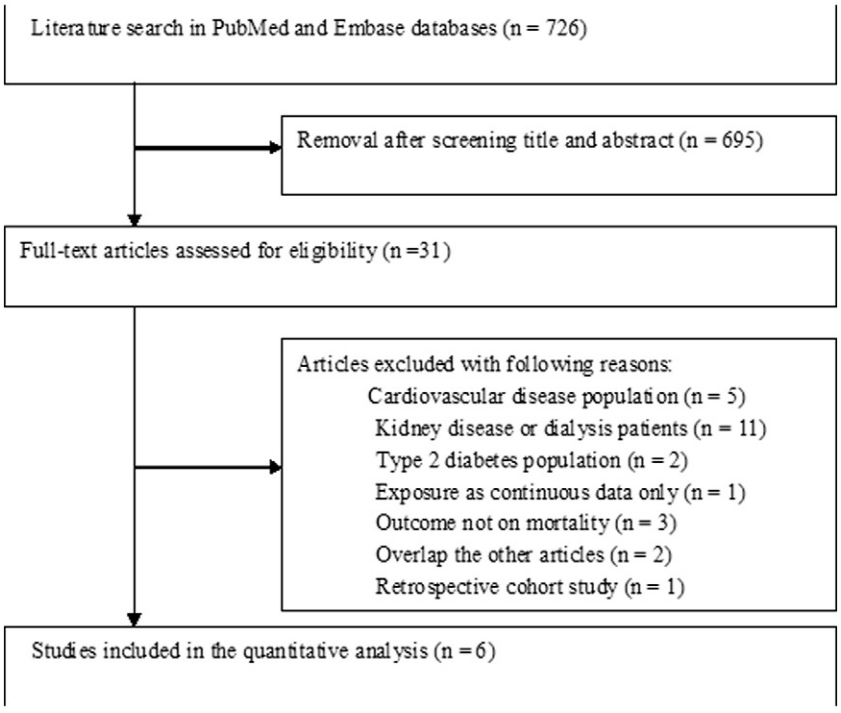

Fig. 1. Flow diagram of study selection process.