Effects of serum phosphorus on vascular calcification in a healthy, adult population: A systematic review

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Cardiovascular disease has been associated with elevated serum phosphorus levels, which have been associated with cardiovascular mortality. This is commonly seen in the chronic kidney disease (CKD) population where studies have shown that high phosphorus levels cause coronary artery calcification. Although studies have independently associated vascular stiffness and serum phosphorus in those with and without CKD, there are fewer data in individuals without CKD. Therefore, the aim of this systematic review was to analyze whether serum phosphorus levels are associated with cardiovascular calcification in healthy individuals. A systematic review of the literature that was conducted revealed 10 articles, all cross-sectional studies, that met eligibility criteria. These criteria were peer-reviewed studies on a healthy, adult population written in the English language. Studies lacking data on serum phosphorus and measured to assess its association with vascular calcification were excluded. Studies on subjects with CKD, other chronic diseases, or on children were also excluded. Of the 10 studies located, 8 indicated an association between serum phosphorus and vascular calcification. One study did not indicate an association. One study indicated a statistically significant association between serum phosphorus and vascular calcification prevalence, but not incidence. Studies were limited since no randomized controlled trials were available. This systematic review generates gaps in research. Due to considerable amounts of phosphorus additives in the food supply, there may be a connection to dietary phosphorus and vascular calcification. Additionally, phosphorus binders may assist in the prevention of vascular calcification but have not been studied in a healthy population. Further study on both dietary phosphorus restriction and phosphorus binders is needed. While 8 out of 10 cross-sectional studies found an association in this systematic review, the topic of vascular calcification and serum phosphorus needs further study if a cause and effect relationship is to be detected. (J Vasc Nurs 2017;35:157-169)

Cardiovascular disease (CVD) is the leading cause of death and disabilities worldwide,[1,2] and epidemiologic evidence has indicated a significant association between elevated serum phosphorus and CVD.[3] Moreover, elevated serum phosphorus itself has been significantly associated with cardiovascular mortality[4] independent of traditional atherosclerotic risk factors.[5] A specific concern as it relates to the alteration of phosphorus metabolism and CVD is vascular calcification, which is the deposition of minerals in the vascular system.[6] Vascular calcification includes intimal and medial calcification as well as calcification of the heart valves.[6] It results in increased arterial stiffness.[6]

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Existing data have demonstrated an association between phosphorus and CVD, namely vascular calcification and arterial stiffness.[4] Myocardial infarction, stroke, and cardiovascular events[6,7] have been associated with vascular calcification, and it has been highly associated with cardiovascular mortality.[6] Furthermore, vascular calcification, which is the calcification in arteries,[8] can lead cardiovascular morbidity and mortality, while medial calcification has been associated with increased all-cause and cardiovascular mortality.[8] While arterial calcification can occur in both the intimal and medial layers of the arteries,[8] the deposition in the medial layer is associated with vascular stiffening[7] and arteriosclerosis.[7,8] Medial calcification is a nonocclusive process that leads to increased vascular stiffness[6,7] and decreased vascular compliance,[6] whereas intimal calcification is associated with atherosclerotic plaque.[7] Decreased compliance of vessels occurs due to medial calcification.[1]

This type of calcification of the arteries, medial calcification, has been associated with increased mortality and is more common in individuals with diabetes, chronic kidney disease (CKD), and advanced aging.[8] Nonetheless, studies have independently associated serum phosphorus with CVD[1,7] and vascular stiffness[7] in those with and without CKD.[1,9] The association between serum

phosphorus and CVD has been noted even at moderately elevated serum phosphorus levels independent of estimated glomerular filtration rate (eGFR).[9] Post hoc analysis of the CARE (Cholesterol and Recurrent Events) study has been noted to show that CVD events were associated with each 1 mg/dL greater serum phosphorus above 3.5 mg/dL (1.13 mmol/L).[9] This association was independent of eGFR and associated CVD risk factors.[9] Normal serum phosphorus levels ranged from 2.5 to 4.5 mg/dL[9] (0.8075-1.45 mmol/L). Despite this association, fewer data are available linking serum phosphorus and vascular calcification in healthy individuals without CKD. Therefore, the aim of this systematic review was to analyze whether serum phosphorus levels are associated with vascular calcification in healthy individuals who do not have kidney disease.

METHODS

Eligibility criteria

This systematic review examined studies in a healthy adult population, greater than 18 years of age. Inclusion criteria for studies were those in the above population written in the English language. Exclusion criteria were studies that did not have data on serum phosphorus and a measurement to assess association with vascular calcification. Studies on those with chronic disease or children were not included nor were those not in the English language. Tissue and animal studies were not included.

Search strategy and data management

Studies that have been published in peer-reviewed journals were pursued from PubMed, CINAHL, and Web of Science. Medical Subject Headings (MeSH) were used to seek appropriate articles. Terms searched were used in combination with "phosphorus" and included "calcification," "calcinosis," "arterial stiffness," "calcification, vascular," "calcinosis, vascular," "cardiovascular disease," and "vascular mineralization." In addition, references on the papers located were screened to seek further sources. All studies located within search parameters were uploaded to EndNote Basic, which was used to manage studies. A total of 5,438 studies were located. Studies were available from years ranging 1956–2016. Duplicates were removed, leaving 4,021 studies. Studies with CKD, stage of

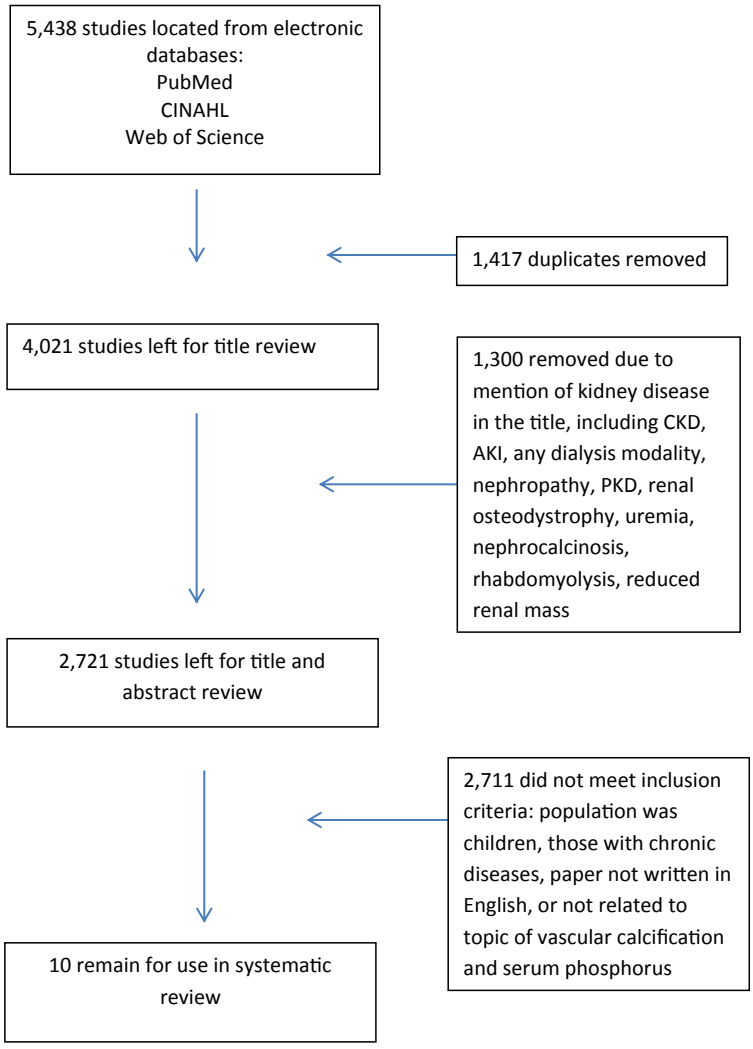

Figure 1. *Literature review and search for articles. AKI = acute kidney injury; CKD = chronic kidney disease; PKD = polycystic kidney disease.*