

## Serum phosphate and chronic kidney and cardiovascular disease: Phosphorus potential implications in general population

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**Author contributions:** Raikou VD wrote this manuscript.

**Conflict-of-interest statement:** The author declares no conflict of interests.

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**Manuscript source:** Invited manuscript

**Specialty type:** Urology and nephrology

**Country/Territory of origin:** Greece

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): 0

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### Abstract

It has already been established that in end-stage renal disease, hyperphosphatemia causes soft tissue calcification including vascular calcifications. It has also been supported that there is a connection between increased serum phosphate and morbidity in subjects, who suffer from renal disease. However, studies in these populations conferred mixed results. Several warnings are included in the role of serum phosphorus on cardiovascular disease in normal populations. Homeostasis of serum phosphate is obtained by the cooperation between regulatory hormones, cellular receptors and bone metabolic factors. There is the probability that one or more phosphate regulatory factors, rather than phosphate directly, may be responsible for observed associations with calcification and cardiovascular events in normal populations. Experimental studies have shown that the restriction of dietary phosphate prevents the progression of kidney dysfunction, although high dietary phosphate aggravates the renal function. In the current review, we discuss the role of serum phosphorus on progression of renal dysfunction and cardiovascular outcomes in chronic kidney disease patients and its involvement in important health risks in the general population.

**Key Words:** Phosphorus; Renal insufficiency; Chronic; Dialysis; Cardiovascular diseases

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**Core Tip:** Disordered phosphorus homeostasis in chronic kidney diseases is associated with bad outcomes including cardiovascular morbidity/mortality and progression of renal dysfunction in end-stage of renal disease. Potential health consequences in cardiovascular and kidney disease could be developed in subjects with a high intake of dietary phosphorus despite the apparently normal renal function, due mainly to abnormalities in metabolism and in regulatory factors, rather than to serum phosphorus itself. The maintenance of serum phosphorus in normal range should be obtained.

Grade C (Good): C, C  
 Grade D (Fair): 0  
 Grade E (Poor): 0

**Received:** February 27, 2021

**Peer-review started:** February 27, 2021

**First decision:** May 6, 2021

**Revised:** May 20, 2021

**Accepted:** July 23, 2021

**Article in press:** July 23, 2021

**Published online:** September 25, 2021

**P-Reviewer:** Prasad G, Saracyn M

**S-Editor:** Ma YJ

**L-Editor:** Filipodia

**P-Editor:** Wu RR



**Citation:** Raikou VD. Serum phosphate and chronic kidney and cardiovascular disease: Phosphorus potential implications in general population. *World J Nephrol* 2021; 10(5): 76-87  
**URL:** <https://www.wjgnet.com/2220-6124/full/v10/i5/76.htm>  
**DOI:** <https://dx.doi.org/10.5527/wjn.v10.i5.76>

## INTRODUCTION

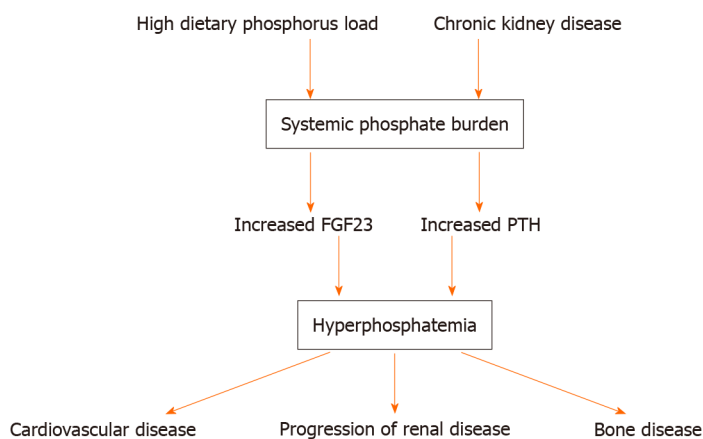
High serum phosphate concentrations have been connected to adverse health outcomes in chronic kidney disease (CKD) including cardiovascular disease, progression of kidney disease and all-cause mortality[1-3]. Hyperphosphatemia in CKD has been also associated with the development of secondary hyperparathyroidism, which is responsible for bone disease implicating the stimulation of regulatory hormones such as fibroblast growth factor-23 (FGF23) and parathyroid hormone (PTH), which in turn may promote left ventricular hypertrophy[4,5]. The kidneys are unable to regulate the serum phosphorus concentrations despite the wide fluctuations in dietary phosphorus intake[6]. In a normal kidney function the phosphorus urinary excretion is increased independently of dietary intake and phosphorus absorption from the gastrointestinal tract and fasting serum phosphate is maintained within a tight range. Therefore, elevation of serum phosphate due to reduced urinary excretion is a main manifestation of advanced renal failure. Previously, we considered the importance of serum phosphate in elderly patients with type 2 diabetes mellitus (T2DM) and we observed the high serum phosphate to be associated with both low estimated glomerular filtration rate (eGFR) and albuminuria, despite the fact that high serum phosphorus levels were found to be non-significant risk factor for the occurrence of T2DM[7]. A positive phosphate balance occurs in the early stage of renal dysfunction, serum phosphate levels mainly increase in advanced stages of CKD and remain elevated in patients in the end-stage renal disease (ESRD) without dialysis treatment (Figure 1).

In the meantime, phosphate is needed in mineralization and bone growth and phosphorus intake is obtained by a rich diet in meat, grains, and dairy products. However, it has been shown that the elevation of serum 1,25-dihydroxyvitamin D [ $1,25(\text{OH})_2\text{D}$ ] concentrations due to low dietary calcium intake is inhibited by high phosphorus intake. Moreover, phosphorus intake may be a major source of acid load in the body[8-10]. Therefore, there remains the question whether high phosphorus intake adversely affects bone mass rather than improves bone function. Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines recommended the maintenance of serum phosphate concentrations within the normal laboratory range in dialysis patients using dietary phosphate restriction or intestinal phosphate binders in order to achieve a such as goal[11]. Several studies have also considered the effectiveness of these approaches in patients with CKD stages 3-5 before the initiation of dialysis[12-17]. It should initiate interventions in early stages of CKD including the control of phosphorus and the use of vitamin D analogs, thus the development of parathyroid hyperplasia and the skeletal complications of CKD to be prevented[18]. Vitamin D analogs are used to suppress hyperparathyroidism having lesser toxicity on calcium and phosphorus than calcitriol. However, it is important that PTH is not over-suppressed, because the decrease of bone turnover to abnormally low levels includes the risk for adynamic renal bone disease, which is combined by exacerbation of extra-skeletal deposition of calcium in blood vessels and other tissues.

In the current review, we discuss the role of serum phosphorus on progression of renal dysfunction and cardiovascular outcomes in CKD patients and its involvement in potential health risks in the general population. We also report evidence for the relationship between dietary phosphate intake and adverse outcomes in these populations.

## RELATIONSHIP BETWEEN SERUM PHOSPHORUS AND PROGRESSION OF KIDNEY DYSFUNCTION

Many years ago, experimental studies showed that the restriction of dietary phosphate prevents the progression of kidney dysfunction, although high dietary phosphate aggravates the renal function[19,20].



**Figure 1** Influence of hyperphosphatemia on different organs/tissues.

However, few clinical studies were conducted to the effect of serum phosphorus concentrations on the rate of CKD progression. It has been shown that in CKD patients serum phosphorus concentrations  $> 4$  mg/dL were associated with an increased risk of ESRD development in both National Health and Nutrition Examination Survey (NHANES) participants and in a United States veterans with CKD study[21,22]. In the Ramipril Efficacy In Nephropathy (REIN) Study, an independent risk of elevated serum phosphorus for exacerbation of renal function in patients with proteinuric CKD was found, although a restriction of the risk was shown caused by the renoprotective action of ramipril[23]. Elevated baseline serum phosphate concentrations were found to be independently related to progression of renal disease in a post hoc analysis of the African American Study of Hypertension and Kidney Disease (AASK) Study[24]. Large study including almost 100000 patients showed that increased serum phosphate concentrations were combined with high incidence of ESRD[25]. Controversially, the Kidney Early Evaluation Program (KEEP) Study did not show an independent association between serum phosphorus concentrations and exacerbation of renal function in ESRD adjusting for demographic and clinical characteristics in multivariable analysis, despite there being a higher prevalence rate of cardiovascular disease (CVD) among patients with higher serum phosphorus[26]. The above studies were different regarding follow-up time and, particularly in the KEEP study, the measurements of serum phosphorus became the baseline and an averaged over time value was not used.

The positive association between serum phosphorus and progression of kidney disease may be attributed to the extension of endothelial dysfunction to the glomerular endothelium, due to acute phosphorus loading, in addition to phosphorus-induced calcification. Another proposed potential mechanism includes the injury of podocytes and overexpression of pituitary-specific positive transcription factor 1 (Pit-1) transporter in rats caused by the elevation of serum phosphorus[27].

Fibroblast growth factor 23 (FGF23) is a hormonal factor, which is significantly involved in maintenance of serum phosphate balance. FGF23 concentrations increase progressively starting in the early CKD as a physiologic adaptation to serum phosphate homeostasis. Eventually, the elevated FGF23 concentrations play an important role on bone disease of these patients[28]. ESRD incidence has also been associated with increased concentrations of FGF23. Studies including participants with mild CKD showed that the risk of all-cause mortality and progression to ESRD was higher in combination with increased FGF23[29,30]. However, a more complicated relationship between FGF23, phosphorus and CKD progression was suggested, due to the association remained stable despite adjustment for phosphorus concentrations.

Accounting for the daily fluctuation of phosphorus, it seems that vascular calcification, endothelial dysfunction, injury of podocytes and high FGF23 result in progression of renal disease, due to high serum phosphorus.

In **Figure 2**, mechanisms which are connected to the relationship between serum phosphorus and the progression of renal dysfunction are shown.

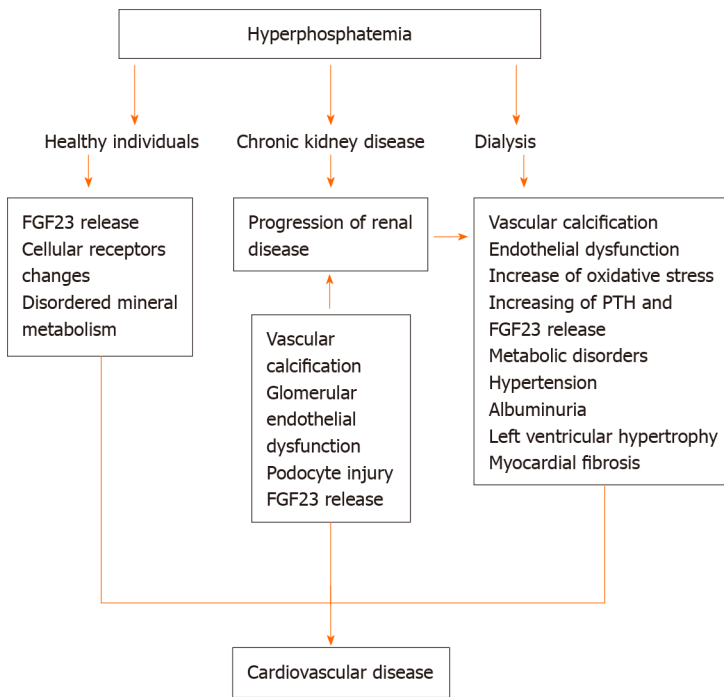


Figure 2 Actions and pathophysiological implications of hyperphosphatemia in different populations.

## SERUM PHOSPHATE AND CARDIOVASCULAR DISEASE IN ADVANCED CHRONIC KIDNEY DISEASE

The patients in advanced CKD present increased calcifications, even those at a young age[31]. It has already been established that in ESRD patients, hyperphosphatemia is the reason of soft tissue calcification including vascular calcifications. Loss of the smooth muscle phenotype, expression of bone-specific markers and mineralization of the extracellular matrix was caused by the addition of exogenous phosphate to cultured vascular smooth muscle cells[32,33]. These processes collectively have as an effect calcification of the medial blood vessel wall (Mönckeberg's arteriosclerosis) resulting in the loss of normal vessel compliance. It has been shown that inferior epigastric arteries removed from ESRD patients undergoing renal transplantation presented medial arterial calcification in a 44% prevalence rate[34,35].

High evidence connecting phosphate overload with medial arterial calcification in renal failure was provided by animal models.

Moreover, it has been highly supported that extended vascular calcification, especially coronary artery calcification may play a potential role in the disproportionately increased prevalence rate of CVD in this population of patients[36]. Many years ago, an independent association between serum phosphate  $\geq 5.5$  mg/dL and all-cause and cardiovascular mortality in hemodialysis patients was shown[37]. Another large study including > 40000 hemodialysis patients showed that serum phosphorus concentrations  $\geq 5$  mg/dL were associated with a high risk of death[38]. However, such an association is not restricted to hemodialysis patients in different countries. A serum phosphate concentration > 3.5 mg/dL was independently associated with mortality and this risk was linearly elevated with an increase in concentration equal to each 0.5 mg/dL in a large retrospective study including 6730 CKD patients from Veterans Affairs Medical Centers[3]. An Italian study including > 1700 CKD patients showed a significant relationship between serum phosphorus and the likelihood of death[39]. Furthermore, the evidence for significant relationship between higher serum phosphorus and mortality in CKD patients was confirmed by a meta-analysis including 47 studies and 327644 CKD participants[40].

Currently, a multinational, randomized controlled large simple trial including a total of 3600 adult ESKD patients receiving dialysis is ongoing with primary endpoints the cardiovascular death, non-fatal major cardiovascular or peripheral arterial events (ClinicalTrials.gov Identifier: NCT03573089). The participants were randomized either to intensive ( $\leq 1.50$  mmol/L) or liberalized (2.0-2.5 mmol/L) serum phosphate target. The choice and dose of phosphate binders is at the treating physician's discretion and local practice to achieve and maintain serum phosphate concentration within the

required target range according to randomization.

Furthermore, HiLo is currently running as another multicenter, cluster-randomized clinical trial of approximately 4400 patients with ESRD undergoing hemodialysis with a primary hypothesis the targeting serum phosphate levels of  $< 5.5$  mg/dL to be compared to less stringent control of serum phosphate to target levels of  $> 6.5$  mg/dL having as a goal the reduction of all-cause mortality and all-cause hospitalization among these patients (ClinicalTrials.gov Identifier: NCT04095039). Secondly, this trial will test if less stringent control of serum phosphate results in increased serum albumin and protein catabolic rate (PCR), as markers of diet and nutrition.

The main mechanism for the relationship between hyperphosphatemia and adverse cardiovascular outcomes has been attributed to vascular calcification caused by phosphorus, but there may be additional potential explanations including acute endothelial dysfunction particularly in cases of an acute elevation of serum phosphorus. It has been used a diet containing either low (400 mg) or high (1200 mg) phosphorus and serum phosphate concentrations were measured before and 2 h after the meals in combination with flow-mediated dilation of the brachial artery measurement. It was found that the high dietary phosphorus load increased serum phosphorus at 2 h (by an average of 0.8 mg/dL) and significantly decreased flow-mediated dilation (by an average of 4.5%) [41]. Such a finding supports that a significant elevation of serum phosphorus, due to oral phosphorus loading, may be important in the pathogenesis of CVD. We recently considered the importance of serum phosphate in elderly patients with T2DM, strongly related to endothelial dysfunction, *vs* non-diabetes mellitus in relation to renal function [7]. We enrolled 110 subjects and 29 of the participants had T2DM (a ratio equal to 26.4%). We found high serum phosphate to be associated with hypertension, albuminuria, smoking, low estimated glomerular filtration rate (eGFR) and metabolic disorders including higher body mass index (BMI), higher serum glucose and higher uric acid levels, possibly due to phosphorus contribution to diabetes mellitus-induced endothelial dysfunction and/or vascular calcification.

*In vitro* experiments also showed that high phosphorus loading inhibited nitric oxide (NO) production due to increased reactive oxygen species release and endothelial NO synthase inactivation *via* conventional protein kinase C (PKC), resulting in impaired vasodilation [41].

Furthermore, there are reports that phosphorus might result in direct actions on the myocardium, causing fibrosis [42]. Although one such as conception was supported by *in vitro* studies, direct clinical evidence has been provided by studies, which have connected hyperphosphatemia with left ventricular hypertrophy in CKD [43] and ESRD patients [44]. A relationship between high serum phosphorus and arterial compliance, which may indirectly result in left ventricular hypertrophy, has also been reported [45].

High FGF23 concentrations have been already found to be a significant risk factor for adverse outcomes including death in patients with CKD [29,46,47]. Higher risk of heart failure, stroke, and death among individuals with preserved renal function were also associated with increased FGF23 concentrations [48].

According to the above, calcification of the medial blood vessel wall (Mönckeberg's arteriosclerosis), endothelial dysfunction and inhibition of nitric oxide (NO) production caused by increased reactive oxygen species release, mainly in cases of acute overload of phosphorus, are involved in the pathophysiological mechanisms of CVD in advanced CKD due to phosphorus. Regulatory factors of serum phosphorus including FGF23 are also implicated in bad outcomes in these patients and high phosphorus may have an additional direct action on myocardium inducing fibrosis (Figure 2).

## SERUM PHOSPHATE AND CARDIOVASCULAR DISEASE IN EARLY RENAL DYSFUNCTION AND IN GENERAL POPULATION

A connection between increased serum phosphate and adverse outcomes in patients who suffer from mild to moderate renal dysfunction or even in subjects who have apparently a normal kidney function has been supported. However, studies in these populations conferred mixed results. Among 3490 male United States veterans with stage III-IV CKD it was demonstrated that there is a significant relationship between higher serum phosphate concentrations and mortality and incident myocardial infarction [3]. Controversially, another previous study did not find any adjusted association of serum phosphate concentrations with all-cause mortality or progression of

renal dysfunction among 10672 individuals who had early CKD in the community-based Kidney Early Evaluation Program (KEEP)[26]. Different demographic characteristics, causes of CKD, comorbidities and the timing of serum phosphate measurements, which vary throughout the day as 1.0 mg/dL, may have contributed to heterogeneous associations[49]. Data from the CARE (Cholesterol And Recurrent Events) study showed an independent association between increased phosphorus and risk of mortality in subjects who had undergone a myocardial infarction[50]. It is worth mentioning that most of the enrolled patients in this study had baseline serum phosphate in normal range and the baseline eGFR was more than 60 mL/min per 1.73 m<sup>2</sup>. Supportively, a number of large epidemiological studies have suggested that mild elevations of serum phosphorus even within the normal range are associated with the risk of CVD including cardiovascular events, vascular calcification and cardiac valve calcification in general population[51-54]. Interestingly, a previous study found that the risk of mortality increases by 1.09 (HR: 1.09; 95%CI: 1.06, 1.84) per every 1.0 mg/dL increase in serum phosphorus considering the relationship between elevated serum phosphorus concentrations over time and mortality in participants with eGFR > 60 mL/min per 1.73 m<sup>2</sup>[25]. Another study found that young men and women with relatively high serum phosphate concentrations (> 3.9 mg/dL) had a greater prevalence rate of coronary artery calcification 15 years later[55].

Many warnings are included in the role of serum phosphorus on CVD in normal populations. Phosphate homeostasis is obtained by regulatory hormones, cellular receptors and bone metabolic factors[56-58]. Common genetic variants located within or near multiple genes of mineral metabolism have been identified, which were associated with serum phosphate concentrations among 16264 individuals without apparently kidney dysfunction[59]. It is probable that one or more regulatory factors of phosphorus, rather than phosphate directly, may be responsible for observed associations with calcification and cardiovascular events in normal populations.

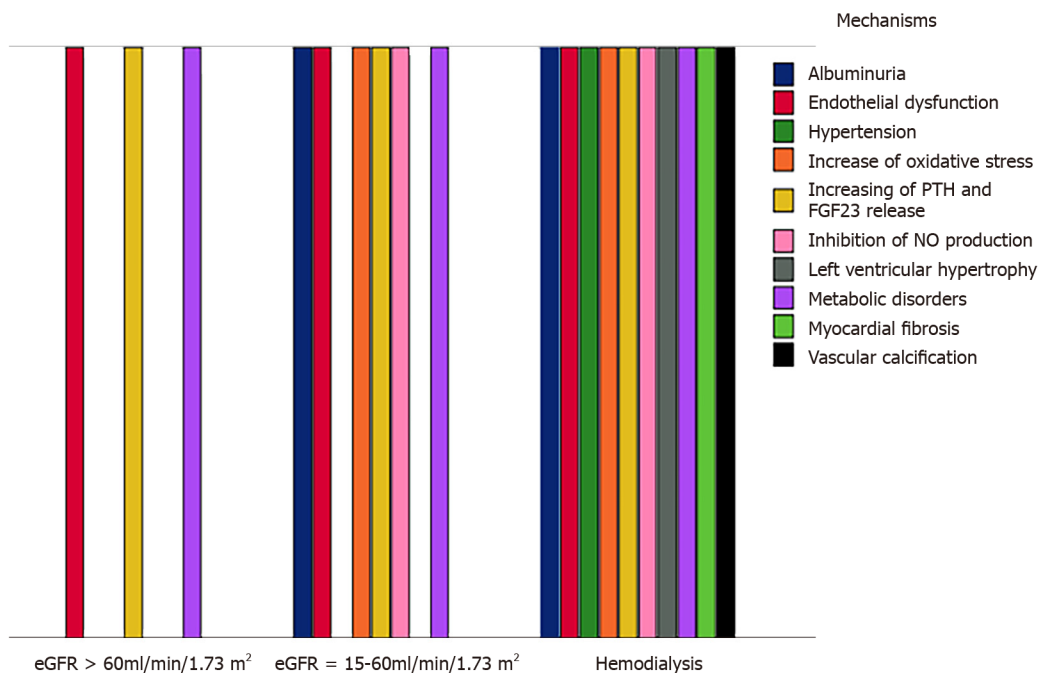
On the other hand, in early CKD and general populations the range of serum phosphate concentrations is typically found within or just above the normal laboratory range. In experimental models higher concentrations of phosphorus were used to induce calcification, ruling out the manifestation of calcification to be a plausible mechanism for the observed associations between serum phosphorus and cardiovascular events in normal populations. Coronary artery calcium represents calcified atherosclerosis rather than medial arterial calcification in normal populations in contrast to advanced renal disease population of patients[60].

Findings related to the risk due to high phosphorus were shown to be controversial in early stages of CKD, because of different demographic characteristics, causes of CKD, comorbidities and the timing of serum phosphate measurements, which vary throughout the day. One or more phosphate regulatory factors including FGF23 and/or cellular receptors, due to genetic variants linked to multiple genes of mineral metabolism, rather than serum phosphate itself directly, are responsible for observed associations between high serum phosphate and both calcification and cardiovascular events in normal populations.

In **Figure 3**, potential mechanisms which are involved to the relationship between serum phosphorus and cardiovascular disease in different stages of renal dysfunction are shown.

## IMPORTANCE OF DIETARY PHOSPHORUS INTAKE

Previous studies have supported that the elevated dietary phosphorus intake is connected to endothelial dysfunction[41] and increased FGF23 concentrations[61]. Particularly in subjects with a normal kidney function it has been shown a significant relationship between high FGF23 Levels and acute oral phosphorus loads[62]. In disagreement, in the Chronic Renal Insufficiency Cohort (CRIC) Study an association between dietary phosphorus intake and FGF23 concentrations was not found[63]. It seems that the interrelation between FGF23 and phosphorus intake is influenced by the kidney function and a preserved kidney function rather than CKD is required thus the association between them to be significant. Moreover, the usage of foods containing inorganic phosphorus additives confuses the results, because inorganic phosphorus is not captured completely by dietary surveys resulting in invalid findings regarding the association between FGF23 and dietary phosphorus intake. On the other hand, a strong, independent association between dietary phosphorus intake and left ventricular mass assessed by magnetic resonance was shown in MESA (Multi-Ethnic Study of Atherosclerosis) Study[64]. Increased oral phosphorus load was also found to



**Figure 3** Mechanisms, which are involved to the relationship between serum phosphorus and cardiovascular disease in different stages of renal dysfunction.

promote the generation of tumors and a significant association between phosphorus and cancer may occur[65].

According to above discussed, the elevated intake of dietary phosphorus seriously disrupts phosphate homeostasis in healthy individuals. A disordered phosphorus homeostasis has potential health consequences in bones, cardiovascular, and kidney disease, even in the presence of reserved kidney function. Furthermore, the increased serum phosphorus, even without elevated oral phosphorus intake, as in advanced CKD patients, may be linked to worse outcomes.

The dietary phosphorus intake is reflected by the serum phosphate concentrations in dialysis patients. It has been established that a significant fall in serum phosphorus is clearly obtained by the restriction of dietary phosphorus or the use of oral phosphate binders[66]. Therefore, serum phosphate levels could be used as a marker of dietary intake in this population. However, a such as relation has not been completely established in CKD patients without dialysis or in normal population, despite a cross-sectional study in NHANES III which showed a mildly significant association between dietary and fasting serum phosphorus concentrations[67]. Since kidney function maintains the balance of serum phosphorus independently on phosphorus intake, fasting serum phosphorus is a very poor indicator of dietary phosphorus intake in normal population or in patients without dialysis. In these subjects repeated measurements of serum phosphorus throughout the day could reflect the wide fluctuation in phosphorus intake.

Moreover, it has been shown a circadian variation of serum phosphorus in healthy subjects and in patients with early renal failure[49,68]. The phosphorus concentrations might vary to 2 mg/dL during a 24-h time. It has been proved that the lowest serum phosphate concentration is in morning specimens and the least difference in serum phosphate concentrations on high- compared with low-phosphate diets also to be at this time of day, without an increase of urine phosphate excretion, PTH or FGF23 to be combined[49]. The mechanisms for phosphorus circadian variation phenomenon are still unclear. Nevertheless, the high variation of serum phosphorus during daytime, due to high oral phosphate load, could result in adverse outcomes, even in normal kidney function[41]. Other factors which influences the relation between dietary phosphorus intake and serum phosphate levels may be the use of foods with additives containing inorganic phosphate and the different bioavailability of phosphorus from various food sources. Phosphorus in meat can be absorbed more than the same amount of phosphorus in cereals. The ratio between calcium and phosphorus dietary intake is also other confounder in the relation between intake and serum phosphorus concentrations.

Table 1 Dietary phosphorus recommendations
<b>Dietary phosphorus recommendations</b>
Restricting dietary phosphorus intake in dialysis patients, thus serum phosphate levels to be maintained within normal range with the use of intestinal phosphate binders or intensive hemodialysis
Restricting dietary phosphorus intake in adults CKD stages 3-5, thus serum phosphate levels in repeated measurements to be maintained within normal range with the use of intestinal phosphate binders
Consideration of bioavailability of phosphorus sources (animals, vegetables, additives) in patients with CKD stages 1-5
Control of serum phosphorus to be in normal range in healthy individuals
Prescribing a high phosphorus intake (diet or supplements) in adult kidney transplant recipients with hypophosphatemia, because a severe drop in serum phosphorus 1.5 mg/dL or below can cause neuromuscular disturbances, due to impaired cellular metabolism

CKD: Chronic kidney disease.

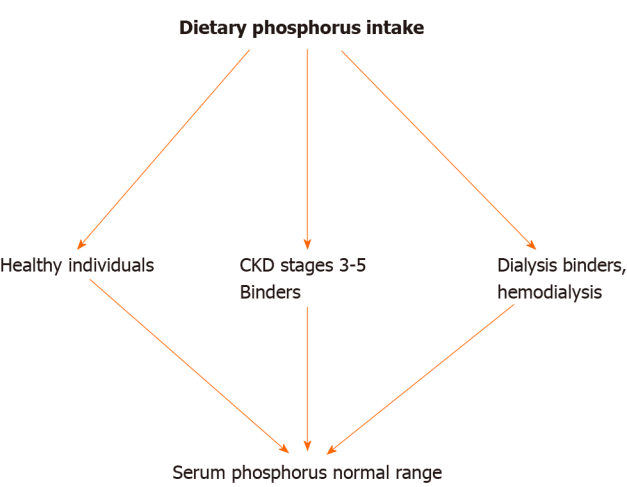


Figure 4 Phosphate control is schematically depicted in different populations.

Although many observational studies have been conducted on the relation between serum phosphorus concentrations/dietary intake and outcomes, it still remains undetermined whether phosphorus is a real toxin or is a simple marker for adverse events. The cause for this would be the lack of a reasonable approach. However, clinical studies including The Modification of Diet in Renal Disease (MDRD) study observed a significant reduction in the risk of ESRD or death with reduced dietary protein intake and, by extension, reduced intake of dietary phosphorus, as the main intervention[69,70]. Even though the comparisons of randomized groups in previous studies do not prove a beneficial cause effect of either protein restriction or phosphorus restriction on morbidity/mortality, such a restriction should be recommended, thus serum phosphorus could be retained within normal range for the reduction of risk for cardiovascular events and the protection of renal function.

In Table 1, recommendations of dietary phosphorus are listed and in Figure 4, phosphate control in different populations of patients are included.

CONCLUSION

Disordered phosphorus homeostasis in CKD is associated with bad outcomes including cardiovascular morbidity/mortality and progression of renal dysfunction in ESRD. Elevated intake of dietary phosphorus seems to disrupt phosphate homeostasis even in healthy individuals, due mainly to abnormalities in regulatory factors including FGE23 connected to genetic variants of mineral metabolism multiple genes, eventually resulting in potential health consequences in bones, cardiovascular, and kidney disease. Therefore, the maintenance of serum phosphorus in normal range should be obtained. However, further studies are still required to clarify the underlying pathophysiologic mechanisms and, particularly, to define interventions,

which would attenuate the adverse outcomes due to phosphorus.

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