Dietary phosphorus restriction in predialysis CKD: time for a cease-fire?

Pieter Evenepoel[1], Marc Vervloet[2]

[1] KUL Leuven, Department of Immunology and Microbiology, Laboratory of Nephrology, B-3000 Leuven, Belgium
[2] VU University Medical Center department of Nephrology and Institute for Cardiovascular Research-VU, Amsterdam, The Netherlands

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Address for correspondence: P. Evenepoel, MD, PhD

Dienst nefrologie

Universitair Ziekenhuis Gasthuisberg

Herestraat 49

B-3000 Leuven

BELGIUM

Tel. +32-16-344591

Fax. +32-16-344599

e-mail: Pieter.Evenepoel@uzleuven.be

Abstract

The increased awareness that disorders of phosphorus metabolism occur early in the course of chronic kidney disease, fuels interest in early intervention strategies. A post-hoc analysis of data from the MDRD questions the clinical relevance of early dietary phosphate restriction, so far considered a mainstay in the prevention and treatment of a mineral metabolism disorders. Although this clinical practice may be called into question, it is premature, based on available evidence, to justify a cease-fire in the war on dietary phosphate.

Key words: diet, phosphate

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Editorial commentary

A large body of evidence links disordered phosphate metabolism with adverse renal and cardiovascular outcomes[1]. Controlling phosphate metabolism in patients with chronic kidney disease (CKD) has been a major therapeutic challenge for nephrologists for decades. As phosphate metabolism is disrupted early in the course of CKD, a rationale exists for treating this disorder before the occurrence of frank hyperphosphatemia. Treatment options mainly comprise use of intestinal phosphate binders and limiting dietary phosphate intake. Several lines of evidence suggest that these strategies are effective in hyperphosphatemic advanced CKD, but their role in CKD patients with normal or near normal serum phosphate levels is less clear. In a recent pilot trial, phosphate binder therapy appeared to promote rather than attenuate the progression of calcification of the coronary arteries and the abdominal aorta in patients with moderate CKD [2]. Randomized hard endpoint studies evaluating safety and efficacy of a phosphate restricted diet in CKD patients not yet on dialysis are non-existing and unlikely to be initiated in the near future. Thus, the nephrology community will have to rely on observational data for dietary guidance. In this regard, the data of Selamet *et al.* presented in this issue of Kidney Int are highly welcomed[3]. The authors performed a post-hoc analysis of data from the Modification of Diet in Renal Disease (MDRD) study to investigate the relationship between dietary phosphate intake and hard clinical endpoints in CKD stage 3-5. The study was negative in the sense that no association was found between baseline dietary phosphate intake and incidence of ESRD and (CVD-, non-CVD or all-cause) mortality in any of the models tested. In addition, there was no association between dietary phosphate intake and serum phosphate concentration. Importantly, dietary phosphate intake was assessed by 24h urinary phosphate excretion (UPE). This is a major strength of the study, as several data support the thesis that 24h UPE in steady state is a more accurate proxy of dietary phosphorus intake than dietary recall. Indeed, 24h UPE lacks the limitations inherent to dietary history including recall bias and inaccuracy of nutrient databases with regard to phosphate content of common food items[4]. The negative findings by Selamat *et al*. [3]suggest that dietary phosphate restriction confers no health benefits as long as serum phosphate levels are within the normal range. However, before drawing this far-reaching conclusion, it might be wise to carefully

revisit the internal and external validity of the authors' findings, and to weigh them against existing literature.

Major strengths of the MDRD study cohort include the long term follow-up and throughout characterization of the study population allowing for multiple adjustments in the cox-proportional hazards models. Notwithstanding these strengths, it should be emphasized that sample size (n=795) for this kind of epidemiological research is relatively small. O'Donnell et al., for example, enrolled > 100.000 individuals in an observational study with a similar setup to demonstrate a significant albeit modest U-shaped association between dietary salt intake, as assessed by 24h urinary sodium excretion, and mortality[5]. The small sample size also limited the exploration of non-linear relationships between dietary phosphate intake and outcomes. In addition to small sample size, use of single UPE measurements and residual confounding may have contributed to a type I statistical error. One may argue that even when associations in the present study were missed due to lack of power, the (narrow) 95% confidence intervals around the risk estimates at least indicate that associations would be modest at best and clinically irrelevant. This may hold true on an individual level but not on a population level. Although risk estimates of similar magnitude were observed in observational studies exploring the relationship between dietary salt and hard outcomes[5], the clinical relevance of salt reduction is usually not questioned. Given the multitude of risk factors involved these low risk estimates should not be surprising. Evidently, subgroups of patients can be identified benefiting more from dietary measures than others. Like patients with hypervolemia or hypertension who benefit more from dietary salt reduction, CKD patients with hyperphosphatemia probably benefit more from dietary phosphate restriction, as compared to patients lacking these conditions (as were most patients enrolled in the MDRD trial).

The baseline 24h UPE of patients enrolling in the MDRD study was considered to best capture individual's usual (lifetime) phosphate intake. This assumption is questionable. The MDRD Study consisted of two randomized controlled trials to determine the effects of dietary protein restriction and strict blood pressure control. Participants were randomly assigned to follow either a low-protein diet (0.58 g/kg per day) or a usual-protein diet (1.3 g/kg day)[6]. As dietary protein is a major source of phosphate, this intervention may be anticipated to have a profound

impact on dietary phosphate intake as well. It is furthermore uncertain whether participants after completion of the 3 yr-MDRD study returned to their (usual) pre-randomization diet or continued the diet imposed during the study. The validity of the baseline dietary data and 24h UPE as a measure of the usual/cumulative phosphorus exposure may thus be questioned.

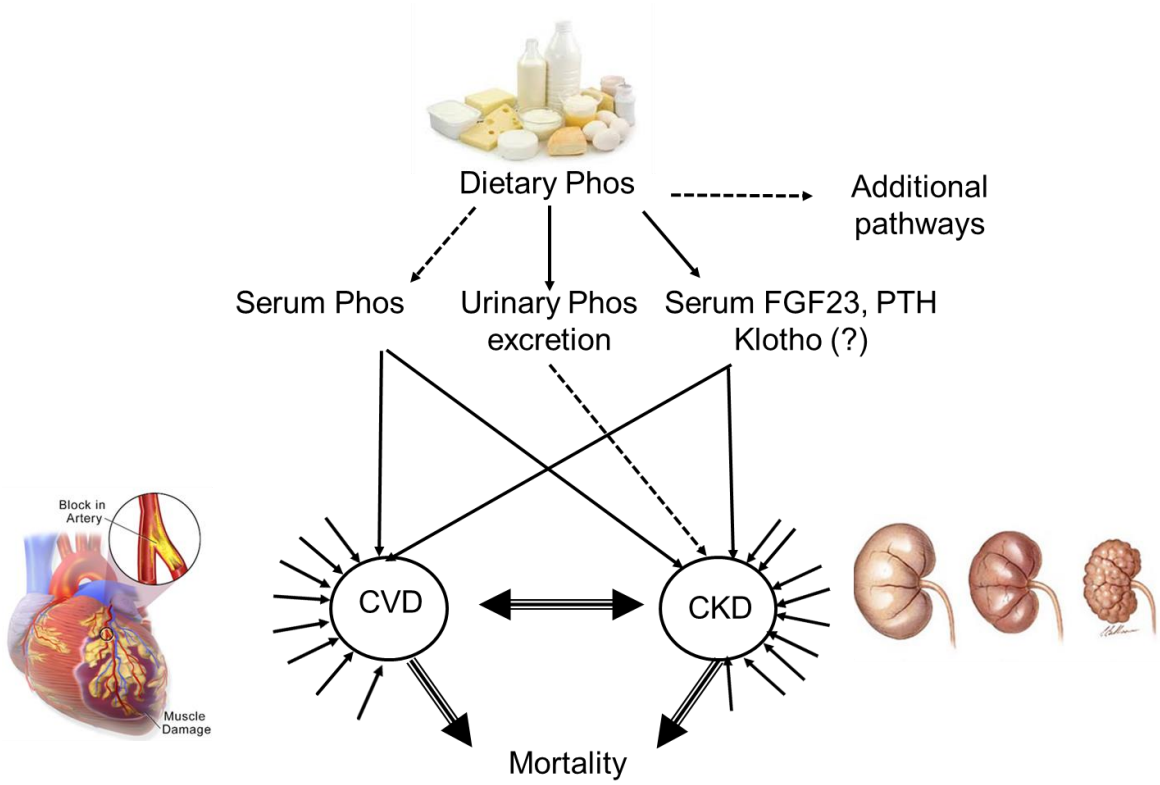
Other concerns relate to external validity. It is important to note that participants to the parent MDRD study[6] were recruited between 1989 and 1993 and that both diet and drug therapy have evolved since then. Dietary phosphate exposure, more specifically, has increased tremendously, mainly as a consequence of the extensive use of phosphate additives by the food industry. Phosphate additives are used in food processing for a variety of reasons, including to extend shelf live, improve color, enhance flavor, and retain moisture. In the 90's, phosphate additives contributed approximately 500 mg/d phosphate to the American diet, whereas today phosphate additives may contribute as much as 1000 mg/d to the average American diet. Dietary phosphate originating from additives and protein differ manifestly, both with regard to bioavailability (100 % vs 60%) and nutritional value (none vs high). Of note, mean baseline 24h-urinary phosphate excretion in a recent intervention trial in healthy subjects, for example, was 1.91 g/day, a value close to the highest exposure observed in the MDRD study[7]. Inhibitors of the renin-angiotensin system (RAAS) are currently more widely used in the daily care of renal patients than in the MDRD trial era. Differences in exposure to RAAS blockade may be relevant regarding patient outcomes considering the increasing body of evidence suggesting crosstalk between phosphate metabolism and the RAAS [8]. Thus, both amount and type of dietary phosphate and relevant drug therapy of patients enrolled in the MDRD study differ from contemporaneous CKD patients, thereby limiting the external validity. This should prompt confirmatory studies.

Phosphate homeostasis is coordinated and regulated by complex cross-organ talk through delicate hormonal networks in which PTH and FGF23 play a crucial role[4]. Compensatory increases of these phosphaturic hormones explain why hyperphosphatemia only occurs when phosphate loading is extreme and/or kidney dysfunction is severe. High PTH and high FGF23 levels associate with poor cardiovascular and renal outcomes, independent of serum phosphate levels. More than 25 years after its conception, the trade-off hypothesis still holds true.

How to translate this evidence to daily clinical practice? The authors rightfully point to limitations of dietary phosphate restriction in the care of normophosphatemic CKD patients and emphasize the need for further studies testing the utility of phosphate reduction strategies. Awaiting the results of these studies (e.g. COMBINE study[9]), dietary phosphate restriction as initial therapeutic measure or as an adjunct to pharmaceutical agents (phosphate binders, NPT2b blockers) in CKD patients presenting with disordered phosphate metabolism remains a valid and defendable approach. Whereas phosphate binder therapy may not be without harm in normophosphatemic CKD patients[2] it is noteworthy and reassuring that the present observational study did not identify safety signals in the lowest dietary phosphate intake quartile. When targeting dietary phosphate restriction, however, focus should clearly be on phosphate additives and not on protein. Such an approach does not hold a threat of protein energy malnutrition and already proved to be feasible and efficacious in dialysis patients. The least what this study should provoke is a cease-fire in the war on phosphate additives.

Figure legend:

Pathways linking dietary phosphorus to chronic kidney disease (CKD), cardiovascular disease (CVD) and mortality. Solid lines denote established pathways; broken lines denote pivotal pathways. Of note, dietary phosphorus is only one out of the many factors impacting on the kidneys and cardiovascular system.



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