Urinary Phosphorus Excretion
Not What We Have Believed It to Be?

Adamasco Cupisti[1] *and Maurizio Gallieni*[2]

Clin J Am Soc Nephrol 13: 973–974, 2018. doi: https://doi.org/10.2215/CJN.06260518

Human phosphate (P) homeostasis includes regulation of intestinal absorption from diet, bone turnover, and urinary excretion, and it is regulated by the combined actions of parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (calcitriol), and fibroblast growth factor 23; the kidney threshold phosphate concentration (TmPO4/GFR) is the main determinant of serum P levels. In the case of significantly reduced GFR, the lower amount of ultrafiltered P strongly impairs its urine excretion capacity by PTH and fibroblast growth factor 23. Thus, in patients with reduced kidney function, a high P load can cause P retention (1).

Under physiologic conditions, the whole-body balance of P is maintained by fine adjustments of urinary excretion to equal the net gastrointestinal absorption (2). This is the reason why measurement of 24-hour urine P excretion has been considered a reliable indicator of net P absorption, which in turn, is related to the quantity and type of P present in the diet. This concept has also been applied to patients with reduced kidney function in a steady-state condition.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Stremke *et al.* (3) question the role and reliability of a single 24-hour urine P measurement as an indicator of dietary P intake and absorption in patients with CKD. In a controlled setting, a 2-week-long balance study including eight patients with reduced kidney function showed that 24-hour urine P measurement has wide day-to-day variability and that the average of at least two 24-hour urine determinations is required for a reliable measurement. In addition, urine P excretion was found to be more tightly correlated with measures of whole-body P balance than intestinal P absorption. In other words, for an individual patient, a low 24-hour urine P excretion may indicate a positive P balance rather than a low net intestinal load, whereas a high 24-hour urine P excretion may be suggestive of a negative P balance rather than a high net intestinal P absorption. However, the results and the conclusions of this elegant and interesting study must not be generalized to avoid the risk of misleading information. First, the conclusion cannot be applied to individuals in the general population with preserved kidney function who efficiently maintain body P balance. In patients with reduced kidney function, the potential reasons for heterogeneity in 24-hour urine P among individuals and day-to-day variation within individuals are numerous. Hence, as the authors themselves appreciated, larger sample sizes are required to confirm the results.

Second, the potential differences in the bioavailability of P from various food sources could have contributed to the wide variability of phosphaturia, but the wide fluctuations within individuals in 24-hour urinary excretion of both P and creatinine may have been influenced by methodologic problems as well. As the authors themselves recognized, incomplete, poorly timed, or inaccurately portioned collections may be potential causes of the wide observed variations as well as problems with measurement of P and creatinine.

Third, equation-based predicted intakes both underestimated and overestimated the measured P intake by as much as 98% and 79%, respectively (3). The lowest predicted P intake was <40 mg/d, and the highest was over 2800 mg/d: these surprising data, especially in a well controlled study setting, may also be affected by under- or overestimation of urine P determination.

The take home message derived from this study is very strong and needs confirmation in two different settings: clinical research and daily practice. In fact, the conclusion that urinary P excretion is of no use or even misleading in the single patient or in observational studies may have an effect on current nutritional management. In everyday clinical practice, phosphaturia is considered a tool for estimation of effective dietary load. On the contrary, the authors suggest that phosphaturia reflects P balance but not the intake: namely, that low 24-hour urinary P excretion indicates P retention, whereas high P excretion reflects P depletion. The authors also speculate that reliability of 24-hour urine excretion can be even worse in the current clinical practice.

Results of the study by Stremke *et al.* (3) are relevant, because they suggest that 24-hour urine P excretion likely reflects not only dietary intake but also, changes in P balance in patients with CKD and reduced kidney function. The reported high variability implies that a single measurement may not give a reliable estimate of urine P excretion. In any case, we should keep in mind that these results apply to patients with stage 3b–4 CKD.

Hence, the important role of 24-hour urine P excretion in subjects with preserved kidney function and patients with CKD who undergo dietary or pharma-

[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; and [2]Department of Clinical and Biomedical Sciences "Luigi Sacco," University of Milan, Milan, Italy

Correspondence: Prof. Adamasco Cupisti, Department of Clinical and Experimental Medicine, University of Pisa, Via Roma 67, 56126 Pisa, Italy. Email: adamasco.cupisti@med.unipi.it

cologic interventions remains valid provided steady-state conditions.

Morimoto *et al.* (4) reported that, in subjects with preserved kidney function, the 24-hour urine P excretion can be used to estimate the dietary P intake and that it may be even superior to estimates on the basis of weighed dietary records. Accordingly, Trautvetter *et al.* (5) reported no difference between the estimated P intake from urinary excretion and weighed dietary records, and they concluded that 24-hour urine collections should be used to assess the phosphorus intake. This is in accordance with the results of Sun *et al.* (6), who evaluated the variability of several urinary biomarkers, including phosphorus, in the United States general population. They concluded that 24-hour urine measurements are potentially useful for the assessment of nutritional exposures, including phosphorus, in epidemiologic studies. Two to three samples of 24-hour urine collections are sufficient to achieve a reliability index >80% for evaluation of chronic intakes (6).

From this perspective, one of the conclusions of the study, namely the poor reliability of phosphaturia as an indicator of P intake/absorption, must be limited to the single measurement in the cross-sectional population-based study including patients with reduced kidney function.

The hypothesis that urine P excretion may be an inverse indicator of P balance in patients with stable conditions remains difficult to accept, although we agree that 24-hour urine P excretion may not always be a reliable estimate of P dietary content. In fact, it should equal net intestinal absorption, which is influenced by a number of factors other than dietary P content. Namely, P from plants sources is less digestible and hence, less bioavailable than P from animal sources; processed food with P-containing additives has the maximum potential bioavailability; concomitant use of active vitamin D and/or P binders, different cooking methods or industrial food processing may differently affect the effective P load (7).

Scanni *et al.* (8) showed that even inorganic P administered by duodenal infusion is not totally found in urine: only 73% is excreted, whereas 100% is retrieved in urine when administered by intravenous infusion, showing that, in normal subjects, the kidneys are able to excrete the effective P load and that bioavailability is not only a function of digestibility (8).

In conclusion, a single 24-hour urine P measurement may be an unreliable marker of P intake in cross-sectional studies including subjects with reduced kidney function. Despite this, 24-hour urine P measurement should still be mostly what we have believed it to be, namely an indicator of net P absorption, in steady-state conditions. Although the relationships between P intake, digestibility, intestinal absorption, and urinary excretion are complex, the repeated measurements of urinary P excretion still remain of value for CKD care management in the real-world clinical setting. However, especially in patients with stage 3b–4 CKD, a correct interpretation of the results is needed, considering that P balance can be influenced by serum P, PTH, and the dietetic and pharmacologic interventions adopted in the individual patient.

Disclosures

None.

References

1. Vervloet MG, Sezer S, Massy ZA, Johansson L, Cozzolino M, Fouque D; ERA–EDTA Working Group on Chronic Kidney Disease–Mineral and Bone Disorders and the European Renal Nutrition Working Group: The role of phosphate in kidney disease. *Nat Rev Nephrol* 13: 27–38, 2017
2. Blaine J, Chonchol M, Levi M: Renal control of calcium, phosphate, and magnesium homeostasis. *Clin J Am Soc Nephrol* 10: 1257–1272, 2015
3. Stremke ER, McCabe LD, McCabe GP, Martin BR, Moe SM, Weaver CM, Peacock M, Hill Gallant KM: Twenty-four-hour urine phosphorus as a biomarker of dietary phosphorus intake and absorption in CKD. *Clin J Am Soc Nephrol* 13: 1002–1012, 2018
4. Morimoto Y, Sakuma M, Ohta H, Suzuki A, Matsushita A, Umeda M, Ishikawa M, Taketani Y, Takeda E, Arai H: Estimate of dietary phosphorus intake using 24-h urine collection. *J Clin Biochem Nutr* 55: 62–66, 2014
5. Trautvetter U, Ditscheid B, Jahreis G, Glei M: Habitual intakes, food sources and excretions of phosphorus and calcium in three German study collectives. *Nutrients* 10: E171, 2018
6. Sun Q, Bertrand KA, Franke AA, Rosner B, Curhan GC, Willett WC: Reproducibility of urinary biomarkers in multiple 24-h urine samples. *Am J Clin Nutr* 105: 159–168, 2017
7. Cupisti A, Kalantar-Zadeh K: Management of natural and added dietary phosphorus burden in kidney disease. *Semin Nephrol* 33: 180–190, 2013
8. Scanni R, vonRotz M, Jehle S, Hulter HN, Krapf R: The human response to acute enteral and parenteral phosphate loads. *J Am Soc Nephrol* 25: 2730–2739, 2014

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Twenty-Four-Hour Urine Phosphorus as a Biomarker of Dietary Phosphorus Intake and Absorption in CKD: A Secondary Analysis from a Controlled Diet Balance Study," on pages 1002–1012.