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# Feasible Low-Phosphorus Dietary Patterns in Maintenance Hemodialysis Patients: Need for Original Research

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Nutritional management has classically been regarded as an integral part of therapy for chronic kidney disease (CKD).[1,2,S1–S4] Various dietary constituents are considered,[1,2] but, in the case of CKD–mineral and bone disorders (CKD-MBD), phosphorus (P) load and hyperphosphatemia have frequently been the focus of attention. Higher plasma P levels (even within the normal range) have been associated with increased risk of incident CKD, vascular calcification, and cardiovascular morbidity and mortality.[3] Moreover, the role of P load and/or hyperphosphatemia in the pathophysiology of secondary hyperparathyroidism, renal osteodystrophy, left ventricular hypertrophy, accelerated progression of CKD, cardiovascular damage/calcification, and aging—via both direct and indirect effects—is supported by compelling epidemiologic and experimental evidence, and biologic plausibility.[3,S5,S6]

The 2017 Kidney Disease: Improving Global Outcomes clinical practice guideline update for CKD-MBD[4] suggested lowering elevated P levels "toward" the normal range (Evidence 2C), and proposed that decisions about P-lowering treatment should be based on progressively or persistently *elevated* serum P (not *graded*). Importantly, and in marked contrast to the level of evidence provided by the recently published National Kidney Foundation (NKF) guidelines for nutrition in CKD,[2] the Kidney Disease: Improving Global Outcomes also *suggested* limiting dietary P intake in the treatment of hyperphosphatemia alone or in combination with other treatments (Evidence 2D). Moreover, in both guidelines it was considered reasonable to consider P source (e.g., animal, vegetable, additives) when making dietary recommendations (not graded, opinion). Because the level of evidence for these interventions is still surprisingly disputed,[2,4] firm dogmatic conclusions do not yet seem possible.[S7] Furthermore, the optimal target for serum P in CKD remains to be defined, and we now know that the priority assigned to lowering serum P should be individualized and may differ depending on many factors.[5] Nevertheless, all guidelines concur that randomized clinical trials (RCTs) are needed to unequivocally demonstrate that treatments aimed at lowering serum P will improve hard- or patient-centered outcomes.[4,S2–S4]

A few short-term RCTs, some very old and relatively small, have evaluated the effect of lowering P intake or in combination with a low protein diet in CKD 3–5D.[S8–S11] According to a recent Cochrane review,[6] there is limited interventional evidence that these dietary interventions may positively affect CKD-MBD,[6] and low certainty that dietary modification makes any difference to clinical outcomes such as quality of life, fractures, cardiovascular events, or mortality. Similarly, in large observational cohorts, dietary intake or modification led to reduced urinary P excretion but did not significantly change either serum P or serum fibroblast growth factor 23 (FGF23) levels, and it remained unknown whether there were beneficial clinical oucomes.[4,S12–S14] Somewhat surprisingly, the recent NKF guidelines[2] *recommend* (Evidence 1B) adjusting dietary P intake to maintain serum P in the *normal range* in adults with CKD 3–5D. Thus, there is a remarkable disparity in evidence level (Evidence 1B vs 2D) compared

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with the Kidney Disease: Improving Global Outcomes guidelines,[2,4] but the latter nevertheless still consider dietary P restriction to be an important standard of practice to lower *elevated* P levels, as several lines of evidence suggest that this strategy may be effective at least in *hyperphosphatemic* advanced CKD or maintenance hemodialysis (MHD) patients.[4,7] For this reason, a "cease-fire" in the war on dietary P has been considered premature,[7] and the need for RCTs to address the effects of various dietary interventions for patients with CKD-MBD has been emphasized.[4,7]

In this issue of the journal, Byrne et al.[8] analyze, in a *pilot* RCT, the short-term (1-month) efficacy, safety, and tolerability of an Irish national *standard* versus *modified* low-P diet in 74 MHD adults, with an average serum P of >5 mg/dl over the last 3 months (mean baseline of 5.92 and 6.13 mg/dl, respectively). Of note, because of the pragmatic nature of the study, fasting and nonfasting blood samples were collected, likely influencing these P levels and masking the basal effect of the standard low P diet. The standard diet restricted pulses, nuts, whole grains, and other high P foods, whereas the modified diet replaced some meat with plant-based vegetarian proteins and unsalted peanuts, increased the use of whole-grain breads and cereals, included egg whites (very low ratio of P/protein), and had an increased focus on the avoidance of P additives.

At first glance, the results of this small study may seem somewhat disappointing with regard to the primary goal of reducing P and/or FGF23 levels. The non–statistically significant small decreases in serum P (−0.336 and −0.295, respectively) may be attributable to not only high individual variability but also the fact that some of the changes would have increased total P intake. However, beyond offering helpful methodologic contributions relevant to the design of future RCTs, this pragmatic study underlines the possibility of a significantly wider food choice (even including previously "prohibited" products), without a resultant increase in P or K levels in an era when patient-centered approaches to treatments must be considered. This greater choice may also improve adherence.[S15] Moreover, the modified diet provides the advantages and potential pleiotropic beneficial effects of an effective higher dietary fiber intake (a significant increase in bowel movements was reported).[S16]

As the authors point out, nutrition science is moving toward dietary patterns instead of individual food nutrients.[S17–S21] In particular, the Mediterranean, New Nordic, and the Dietary Approaches to Stop Hypertension diets have shown beneficial effects in preventing and managing renal disease, at least in selected adherent individuals.[S18–S21] Both the Mediterranean and the Dietary Approaches to Stop Hypertension diets overlap in nutritional composition, encouraging whole foods such as fruits, vegetables, pulses, whole grains, and nuts.[S17] In addition, these diets restrict animal protein consumption and limit processed and fast foods.[S17] However, in later CKD stages and in patients on MHD, the prescribed dietary pattern needs to be more carefully individualized for specific nutrients (i.e., P, K, and/or protein content). For instance, traditional dietary CKD recommendations limit the intake of fruits and vegetables because of their high K content. Nevertheless, this paradigm is rapidly changing.[S22–S24] A higher fiber content, acidosis neutralization, decreased P absorption, increased magnesium and vitamin K, and even improvement in gut dysbiosis and reductions in inflammation and oxidative stress, have been observed with vegetarian diets (and adequate cooking techniques).[S24] In their study,[8] the authors somewhat altered their standard renal diet toward a locally adapted Mediterranean dietary pattern, retaining the ability to individualize nutrient restrictions without affecting serum K. Considering that, on a global scale, there are quite significant differences in diet compositions and food availability, such pattern modifications seem of great interest. Similarly, some modifications have recently been made to the New Nordic diet in order to decrease its P content and absorption, although these have been tested for only 1 week in non-dialysis CKD patients.[9]

Another important piece of information provided is the infrequently reported *phytate-bound* P (significantly higher in the modified diet). Thus, dietary P sources were divided into foods with P that is or is not bound to phytate. Estimates of dietary P from food composition tables likely underestimate the P content because they mostly reflect the "natural" P content of foods, but composition and absorption may differ according to food processing. Moreover, especially in patients lacking kidney function, it is very important to consider the *bioavailability* of P based on its sources (organic vs. inorganic).[S25] Nephrologists should be aware of the almost 100% bioavailability of inorganic P (such as in additives) and the reduced bioavailability of organic P in plant foods due to the limited absorption of phytate-based P in the human gastrointestinal tract (owing to the lack of the enzyme phytase, necessary to degrade

dietary phytate and release P).[S25] Therefore, many of the foods traditionally labeled as containing high amounts of P (e.g., beans and nuts) may be acceptable as protein sources in view of their low absorption rate (K permitting). The potential importance of considering phytate-bound P is stressed by our recent study demonstrating that an intravenous formulation of phytate (SNF472) significantly attenuated the progression of coronary artery and aortic valve calcification in MHD patients.[S26] Dietary regimens prescribed for MHD patients reduce the intake of many of the main phytate-containing foods.[S27] In experimental and some human studies (mostly observational), phytate has been associated with several beneficial properties.[S27]

Beyond the many strengths and certain weaknesses of the study (i.e., short-term, heterogeneity of P measurements), it should be recalled that dietary P restriction may be difficult without compromising the intake of other nutrients, especially protein, with the threat of protein-energy wasting. Protein intake was lower than recommended in both RCT arms despite the introduction of some pulses and nuts. Although the apparent reduced protein intake may be due to underreporting, and is unlikely to be of a different magnitude when comparing both arms, it may represent a safety signal that should be closely followed. In fact, there is general agreement that, when targeting dietary P restriction for MHD patients, the focus should clearly be on P additives and not protein.[7] Therefore, although the authors describe no significant differences in protein intakes, weight, predialysis urea, or baseline urea reduction ratio between the 2 groups, in upcoming studies it would be most helpful to closely follow up body composition and other nutritional parameters.[2] Hopefully, these dietary regimens will be used, at least in selected MHD patients, over long periods, and it must be demonstrated that the prescribed diet is sustainably tailored to patients' needs and habits. Finally, it remains to be proven whether the addition of P- or K-binders may improve results without significantly interacting with other drugs, the absorption of other nutrients, or the intestinal flora.[S24,S28,S29]

Although the differing approaches and opinions of medical societies and national guidelines[2,4] are puzzling, the need to undertake challenging RCTs is always acknowledged. In this context, we welcome any information, such as that derived from this pilot RCT, which may contribute to a more robust and homogeneous approach to the cost-effective nutritional management of CKD 3–5D.[1,8] Rather than enumerating restrictions, it may soon be possible to design individualized dietary patterns with clearly significant benefits in terms of clinical outcomes, or at least patient-related outcomes.

## DISCLOSURE

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Supplementary References**.

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