Published in final edited form as:

Curr Osteoporos Rep. 2017 October ; 15(5): 473–482. doi:10.1007/s11914-017-0398-4.

Effects of Excessive Dietary Phosphorus Intake on Bone Health

Colby J. Vorland, MS,
Department of Nutrition Science, Purdue University, West Lafayette, IN

Elizabeth R. Stremke, BS,
Department of Nutrition Science, Purdue University, West Lafayette, IN

Ranjani N. Moorthi, MD, and
Department of Medicine-Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN

Kathleen M. Hill Gallant, PhD, RD
Department of Nutrition Science, Purdue University, West Lafayette, IN

Department of Medicine-Division of Nephrology, Indiana University School of Medicine, Indianapolis, IN

Abstract

Purpose of Review—The purpose of this review is to provide an overview of dietary phosphorus, its sources, recommended intakes, and its absorption and metabolism in health and in chronic kidney disease, and to discuss recent findings in this area with a focus on the effects of inorganic phosphate additives in bone health.

Recent Findings—Recent findings show that increasing dietary phosphorus through inorganic phosphate additives has detrimental effects on bone and mineral metabolism in humans and animals. There is new data supporting an educational intervention to limit phosphate additives in patients with chronic kidney disease to control serum phosphate.

Summary—The average intake of phosphorus in the US well-above the recommended dietary allowance. Inorganic phosphate additives, which are absorbed at a high rate, account for a substantial and likely underestimated portion of this excessive intake. These additives have negative effects on bone metabolism, and present a prime opportunity to lower total phosphorus intake in the U.S. Further evidence is needed to confirm whether lowering dietary phosphorus intake would have beneficial effects to improve fracture risk.

Keywords

phosphorus; nutrition; bone; phosphate additives

Corresponding Author: Kathleen M. Hill Gallant, PhD, RD, 700 West State Street, West Lafayette, IN 47907, hillgallant@purdue.edu.

Conflict of Interest
Elizabeth Stremke and Colby Vorland declare no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Phosphorus is an important nutrient for bone health, but intakes in the U.S. usually well-exceed requirements. This is problematic because excessive dietary phosphorus has been associated with adverse effects on bone and mineral metabolism. New literature in this area highlights the effects of a high dietary phosphorus burden from prevalent use of phosphate-based food additives in the U.S. This review provides an overview of the role of phosphorus in bone health, adverse effects of excess intake, and findings from recent studies focused on effects of phosphate additives on bone and mineral metabolism in health, and in the special case of chronic kidney disease-mineral bone disorder.

Phosphorus as an Essential Nutrient

Phosphorus is an essential nutrient in human health and has a variety of physiological roles. These include structural roles, as phosphorous is a major component of cell membranes (i.e. phospholipid bilayer), the sugar-phosphate backbone of nucleic acids, and hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) in bones and teeth. Additionally, phosphorus plays important roles in energy metabolism (e.g. in ATP, GTP, ADP, GDP), in acid/base balance, and in intracellular cell signaling (1). The vast majority of the body's phosphorus is found in bone mineral (approximately 85%), and the remaining 15% is distributed in soft tissues with about 1% in extracellular fluid (2). Phosphorus deficiency results in rickets and stunted growth in children and osteomalcia in adults. However, dietary phosphorus deficiency is very rare in humans, due to the natural ubiquity of phosphorus in a large array of foods and our high capacity to absorb it. Only in special circumstances, such as starvation, refeeding syndrome, or poorly managed parenteral nutrition is hypophosphatemia observed in otherwise healthy individuals (1). Thus, most cases of phosphorus deficiency result from a defect in renal reabsorption of phosphate. There are a variety of renal hypophosphatemias that are characterized by a low plasma phosphate and a low tubular maximum reabsorption rate of phosphate (TmP). These include genetic disorders that cause either highly increased levels of the phosphaturic hormones, fibroblast growth factor-23 (FGF23) or parathyroid hormone (PTH), or cause defects in the renal tubular sodium phosphate co-transporters that are responsible for phosphate reabsorption (3). Oral phosphate supplements are needed as part of treatment for these patients. Outside of these specific patient groups, humans are usually able to easily consume adequate phosphorus from a variety of foods.

Dietary Phosphorus Intake and Sources

The most recent Dietary Reference Intakes (DRIs) for phosphorus in the United States were established by the Institute of Medicine in 1997 (1). These include the estimated average requirement (EAR), the intake level estimated to meet the needs of 50% of healthy individuals in a group (age/sex/life stage), and the recommended dietary allowance (RDA), the intake level estimated to meet the requirements of 97.5% of healthy individuals in a group. Phosphorus is present in foods in naturally-occurring forms in meats, nuts, seeds, legumes, dairy foods, and grains, as well as in inorganic phosphate additives that are used for a variety of purposes in food processing. Because phosphorus is so widespread in the food supply both naturally and from additives, most people do not have difficulty meeting

intake requirements and dietary phosphorus deficiency is extremely rare. Instead, usual dietary intakes generally well-exceed recommended intakes. Data from the National Health and Nutrition Examination Survey (NHANES) 2005–2006 show that this is true for males and females across all age groups, except for adolescent women ages 9–18 years old, whose average intake is similar to the EAR (4). In healthy adults, the phosphorus EAR is 580 mg/d and the RDA is 700 mg/d (1). However, the average phosphorus intake of U.S. adults over the age of 20 is 1399 mg/d – approximately 2.5 times the EAR and twice the RDA. McClure et al. (5) recently described the trends in dietary phosphorus intake in U.S. adults between 2001–2014 from NHANES data, as well as the percent contributions of various categories of foods to total phosphorus consumption. Although total phosphorus consumption has risen over the recent decades (6), intakes were relatively stable between 2001 and 2014 (5). Grains were the largest contributor to total dietary phosphorus intake, accounting for 29.3% of intake. Other major contributors were milk and milk products (21% of intake) and meat, poultry, fish and mixtures (25% of intake). Despite being considered somewhat of a villain in the phosphorus world, soft drinks contributed only 3.3% to total phosphorus intakes. However, unlike foods like grains, dairy and meats, soft drinks usually provide minimal to no additional nutrients aside from calories and sugar (7). Further, consumption of cola, in particular, is associated with altered bone metabolism, low bone density and fracture in human and animal studies (8–14).

Bioavailability of phosphorus also varies depending on source. Plant protein sources generally have the lowest bioavailability, followed by animal protein sources, then inorganic phosphate additives with the highest bioavailability. Inorganic phosphates have been considered to be nearly 100% bioavailable. However, this might be better described as nearly 100% *bioaccessible* (i.e. what is available for absorption), rather than *bioavailable* (i.e. what is absorbed and available to the tissues) (15). Scanni et al. (16) showed in healthy adults that only 73% of inorganic phosphate infused by nasoduodenal feeding tube was recovered in the urine, compared with 100% of i.v.-infused phosphate. This suggests only 73% of the inorganic phosphate infused into the duodenum was absorbed, despite that the bioaccessibility of sodium phosphate is ~100%. St-Jules et al. (17) further demonstrate the case for less than 100% bioavailability of inorganic phosphate by highlighting the discrepancy between the proportion of phosphorus excreted in the urine versus the amount of phosphate given in multiple human feeding studies.

Regulation of Phosphorus Homeostasis

Phosphorus homeostasis is maintained via a multi-tissue axis involving the kidneys, parathyroid glands, intestine, and bone. The three main hormones responsible for phosphorus homeostasis are PTH, FGF23, and 1,25-dihydroxyvitamin D (1,25D) (18). The normal range of serum phosphate is 2.5–4.5 mg/dL. Transient elevations in serum phosphate cause increased PTH production and secretion, which increases the conversion of 25-hydroxyvitamin D to 1,25D via the renal CYP27B1 (1α-hydroxylase) enzyme. Both PTH and 1,25D stimulate FGF23 production from osteocytes. PTH and FGF23 increase urinary phosphate excretion by inhibiting the renal sodium-phosphate co-transporters (NaPi-2a and NaPi-2c) which results in decreased renal phosphate reabsorption. PTH and 1,25D stimulate bone resorption to release calcium and phosphorus, and 1,25D increases the active

absorption of both calcium and phosphorus from the intestine. Homeostasis is further maintained by negative feedback loops involving these three hormones: FGF23 provides negative feedback on PTH and 1,25D, and 1,25D provides negative feedback on itself and PTH.

Intestinal absorption of dietary phosphorus occurs by both transcellular active transport that is sodium dependent, and paracellular passive transport that is sodium-independent. The major known phosphate transporter in the intestine brush border membrane is sodium-phosphate co-transporter 2b (NaPi-2b), which is a type II sodium-phosphate transporter that shares homology with NaPi-2a and NaPi-2c in the kidney (19, 20). In addition to high levels of phosphorus present in our foods, humans also have generally high phosphorus absorption efficiency, around 60–70 % from a typical mixed diet (21). The major known modulators of phosphorus absorption efficiency are dietary phosphorus, 1,25D, and FGF23. Low phosphorus diets and 1,25D directly increase phosphorus absorption efficiency, while FGF23 decreases phosphorus absorption efficiency indirectly through its inhibition of 1,25D (21, 22). It had been presumed that the effect of low phosphorus diets on increased intestinal phosphorus absorption was mediated by an increase in 1,25D (21, 23). However, low phosphorus diets cause increased intestinal phosphorus absorption even in VDR and CYP27B1 knockout mice (24, 25). This suggests that the effects of low phosphorus diets on increased phosphorus absorption are vitamin D-independent and through mechanisms not yet fully known. Low phosphorus diets and 1,25D both increase NaPi-2b abundance in the brush border membrane. But, low phosphorus diets appear to affect NaPi-2b through both transcription and post-transcriptional mechanisms, whereas the effects of 1,25D appear to be post-transcriptionally mediated (21).

Despite the role of the intestine in absorbing phosphorus, thus making it bioavailable for its many physiological functions, the kidney is the main point of regulation of serum phosphate (26, 27). Scanni et al. (16) recently demonstrated in healthy adults the kidneys' ability to fully compensate for increased absorbed phosphorus load, and that the intestine did not play a noticeable role in this response. However, even if renal phosphate excretion is able to maintain phosphate balance and serum phosphate within normal range, adverse effects of high dietary phosphorus on bone and mineral metabolism are still present.

High Dietary Phosphorus Intake Effects on Bone Health

Early studies in animals show that high dietary phosphorus, particularly with low dietary calcium, reduces bone mass, and that this is mediated by secondary hyperparathyroidism (28–31). Draper et al. (30) demonstrated that parathyroidectomy prevented increased bone resorption in response to a high phosphorus diet in adult rats. More recently, the bone matrix protein osteopontin (OPN) has been identified as another factor that mediates the increased bone resorption response to a to high phosphorus diet. Koyama et al. (32) fed 4-month old OPN deficient and wild-type adult mice a diet of 0.5% calcium with either 0.16% or 0.6% phosphorus for four weeks. OPN deficiency prevented a reduction in bone mineral density and mass, changes in trabecular bone patterns, and cortical bone appearance and area, cross-section, periosteal circumference, and thickness. Bone formation was not affected by OPN deficiency, but the bone resorption response to a high phosphorus diet was prevented. Thus,

the impact of a high phosphorus diet appears to be mediated in part by both OPN and PTH to increase bone resorption.

High dietary phosphorus also adversely affects bone mass accrual during growth. Huttunen et al. (33) fed 1-month-old rats diets of 0.6% calcium and either 0.6%, 1.2%, or 1.8% phosphorus for 8 weeks. The highest phosphorus diets (1.2% and 1.8%) reduced body weight, bone mineral content, and areal bone mineral density. Femur length and PTH were lowered at 1.8% P, and dose dependent decreases of trabecular area, width, and perimeter, and increases of osteoblast perimeter, osteoclast number, and mineral apposition rate were observed. pQCT in the distal metaphysis and midshaft showed a reduced BMC and total cross-sectional area, and tibia material properties were reduced on a high phosphorus diet.

Table 1 summarizes human clinical intervention studies on the impact of high dietary phosphorus intake and bone and mineral metabolism. Most studies show that high dietary phosphorus increases PTH (34–46), and exceptions tend to be studies where dietary calcium intake also increased with higher dietary phosphorus intake (41, 47, 48). The effects on bone turnover markers is more mixed, but when effects are seen they are generally in the direction of increased bone resorption and/or decreased bone formation with higher dietary phosphorus. Observational studies exploring the relationship between high dietary phosphorus and bone endpoints have similarly found mixed results. In large population surveys of the U.S. (49) and South Korea (50), generally no relationships between dietary phosphorus and BMD, BMC, or osteoporosis were observed. Similarly, in perimenopausal women there tended to be no relationship between dietary phosphorus intake and BMD and BMC (but higher dietary calcium and calcium:phosphorus (Ca:P) ratio was positively related to BMD and BMC) (51). In contrast, in a Brazilian cohort with low average calcium intake (~400 mg/d), for each increase of 100 mg/d in dietary phosphorus there was a 9% increase in fracture risk (52). Recently, a combined analysis of the relationship between serum phosphate and fracture risk in the Rotterdam Study and MrOS prospective cohorts was reported by Campos-Obando et al. (53). Serum phosphate was positively related to fracture risk, where there was a 47% increased risk of fracture with each 1 mg/dL increase in serum phosphate after adjusting for multiple covariates. Dietary phosphorus intake was available for a subset of subjects from MrOS, assessed by food frequency questionnaire. In these subjects, fasting serum phosphate did not relate to dietary phosphorus intake, nor did adjustment for dietary phosphorus intake affect the association between serum phosphate and fracture risk. However, as the authors also note, fasting serum phosphate is less sensitive to dietary phosphorus compared to postprandial serum phosphate measures. Additionally, accurate assessment of dietary phosphorus intake from food frequency questionnaires is limited by participant errors as well as incomplete and inaccurate nutrient database content (15). Campos-Obando et al. (53) also note that the increased fracture risk associated with serum phosphate was observed within the normal range for serum phosphate, which may suggest that usual intakes are too high. However, whether dietary phosphorus intake affects serum phosphate levels within the normal range remains unclear.

Recently, Katsumata et al. (54) investigated the effects of high dietary phosphorus bone and mineral metabolism-related gene expression in younger (12-week-old) and older (80-week-old) mice. Mice were fed a diet of either 0.3% or 1.2 % phosphorus, with adequate calcium

(0.5%) for four weeks. Serum PTH increased in both young and old mice in response to the high phosphorus diet, but to a greater extent in the old mice. Femur RANKL mRNA was increased with high dietary phosphorus in both younger and older mice, but the RANKL:OPG mRNA ratio was only increased in the old mice, suggesting that the effects of high dietary phosphorus on bone resorption are more pronounced with aging. In a second study, Katsumata et al. (55) further investigated the effects and interaction between high dietary calcium and phosphorus on bone outcomes in rats. Rats were fed either adequate calcium (0.5%) or high calcium (1.0%) and either adequate phosphorus (0.3%) or high phosphorus (1.5%) in a 2×2 factorial design. High phosphorus diets caused increases in PTH, CTX, osteocalcin, and femur RANKL mRNA, and decreases in femur, tibial, and lumbar BMD and BMC. High calcium with high phosphorus blunted the effects of the high phosphorus diet on PTH, CTX, BMD and BMC measures, and prevented the rise in osteocalcin. The Ca:P intake ratio and its relevance in bone health is discussed below.

Dietary Calcium-to-Phosphorus Ratio

Intake of phosphorus relative to calcium is of interest, as these mineral interact in the gastrointestinal tract to limit absorption of the other, are intimately related in tissue (e.g. hydroxyapatite) and in their hormonal regulation. A 1:1 molar ratio of Ca:P (or ~1.3:1 mass ratio Ca mg:P mg) has been recommended to optimize calcium and phosphorus nutrition for bone health, yet the vast majority (~90%) of U.S. Americans fall below this ratio due to the combination of prevalent low calcium intakes and excessive phosphorus intakes (4). However, the current IOM DRI report for phosphorus, published in 1997 (1), made the case that the dietary Ca:P ratio was not physiologically relevant in human health within the range of dietary phosphorus intakes typically consumed in the U.S. Studies that show associations or effects of low Ca:P ratio on bone metabolism are confounded by low calcium intake coinciding with the low Ca:P ratio. Additionally, classic balance studies in adults have shown that high phosphorus intake does not influence calcium balance or absorption compared with low phosphorus intake, and the level of calcium intake does not modulate this effect (56–58). And a cross-sectional analysis of 215 young women found no evidence for an ideal Ca:P ratio to optimize bone mass (59). However, 20 years since the IOM report, the importance of dietary Ca:P ratio for bone health in humans is still unclear and somewhat controversial (60, 61). Minimally, it appears that dietary Ca:P ratio has to be taken in context of the absolute levels of each mineral in the diet as well (7). However, it is also possible that the ratio is irrelevant, but that low dietary calcium and excess dietary phosphorus can each be independently harmful to bone. Further, the interaction between low dietary calcium and excess dietary phosphorus doesn’t necessarily support the existence of a meaningful ratio independent of the absolute values of each nutrient. Nonetheless, high dietary phosphorus has consistently shown adverse effects on bone-related outcomes in animal studies, and there is human data that also supports an independent effect of high phosphorus intake on adverse bone-related outcomes, although less consistently. In recent years, there has been mounting evidence that shows adverse effects on bone metabolism with increased phosphorus intake from inorganic phosphate additives, which are absorbed rapidly at a high rate.

Phosphate Additives Effects on Bone Metabolism

Inorganic phosphate additives are highly bioaccessible, as discussed above, and have been shown to contribute a substantial amount of phosphorus to total intake in the U.S. (62, 63). Cola is a unique source of additive inorganic phosphate that has been studied over the years in its effect on bone health. Cola delivers a load of phosphoric acid that is absorbed readily and rapidly and is often consumed between meals. A 20 fl. oz. bottle of cola, for example, provides 55 mg of phosphorus, whereas non-cola sodas are phosphate-free. In addition, cola may displace milk in the diet, so it can contribute to lower calcium intake concurrent along with greater inorganic phosphophosphates intake (12). This has been investigated in early and later life stages. Wyshak (13, 14) observed that higher cola consumption has been associated with greater fracture risk in adolescent boys and girls. Tucker et al. (8) found an association between greater cola intake and low bone mineral density in older women in the Framingham Osteoporosis Study, but no association with non-cola carbonated beverages. This supported prior studies in rats that showed impaired bone mineralization and hyperparathyroidism when rats were given cola in place of water (9, 10). However, human observational studies have not consistently shown these associations between cola intake and bone outcomes. There was no association between any type of carbonated beverage consumption and bone mineral density in older women who participated in the Rancho Bernardo Study (11), nor in the men in the Framingham Osteoporosis Study (8), and McGartland et al. (64) found an inverse relationship between non-cola and total carbonated beverage consumption in Irish adolescent girls, but no relationship with cola consumption. It seems likely that any potential negative effects of cola on bone when it substitutes for milk in the diet would be driven by decreased calcium intake and other bone health nutrients (e.g. protein, vitamin D) in milk, rather than the difference in phosphorus load. This is because milk has about ten times the phosphorus content of cola by volume, so even if we assume most liberally that 100% of inorganic phosphate from cola is absorbed and only 40–70% of organic phosphorus from milk, this would still result in ~4–7 times more phosphorus absorbed from the same volume of milk as cola. However, it may be that the additional inorganic phosphate from cola may provide an additional insult to the replacement of nutrient-rich milk in the diet.

A recent study by Gutiérrez et al. (65) further evaluated the impact of dietary inorganic phosphate additives on bone in complementary studies in humans and mice. Participants in the human study were given a “low additive” diet for one week (~1000 mg/d phosphorus), followed by an “additive enhanced” diet for one week (~1600 mg/d phosphorus), with ~700 mg/d of calcium throughout the two week study. After one week on the additive enhanced diet, participants had higher FGF23, osteopontin, and osteocalcin, and lower sclerostin and P1NP. Similarly, mice fed low (0.2%) and high (1.8%) dietary phosphorus higher FGF23, osteopontin, and osteocalcin, lower sclerostin and also lower BMD and unfavorable changes in cortical and cancellous bone geometry by μCT. This study is notable as it shows that diets high in foods containing inorganic phosphate additives at levels typical in the U.S. can adversely alter bone and mineral metabolism.

Special Considerations for Dietary Phosphorus in CKD-MBD

Dietary phosphorus intake is of particular importance in patients with chronic kidney disease (CKD), who develop the co-morbid condition of mineral bone disorder (CKD-MBD). CKD-MBD is characterized by biochemical abnormalities related to bone and mineral metabolism, including elevated serum FGF23, PTH, phosphate, and decreased serum 1,25D and calcium; renal osteodystrophy presenting with a range of abnormalities in bone mineralization, volume, and/or turnover; and increased vascular calcifications. Patients with CKD-MBD have elevated risk for bone fragility fractures, cardiovascular events, and death (71, 72). Patients are often prescribed low phosphorus diets as a component of treatment to slow or prevent CKD-MBD, hyperparathyroidism, or hyperphosphatemia. But, low phosphorus diets are extremely difficult for patients to follow, due to the widespread presence of phosphorus in the food supply, other concurrent nutrient and fluid restrictions, and while attempting to consume adequately high energy and protein. Thus, there has been growing interest in diet liberalization to improve patients' nutrition and quality of life (73). A potential way to limit phosphorus intake in CKD patients without sacrificing overall nutrition and quality of life is to focus interventions at limiting non-nutritive or low-nutritive phosphate sources. Phosphates coming from medications and from inorganic phosphate additives are prime targets for this. Patients with CKD have a high pill burden. Up until recently, the phosphate burden from these patients' medications was unquantified. Nelson et al. (74) evaluated the phosphate content of medications prescribed in hemodialysis patients with advanced CKD. 11% of drug formulations prescribed in the 101 hemodialysis patients in the study contained phosphate, and 30% of patients were taking at least one of these medications. The average phosphate burden from prescription medications in this study was 111 mg/d. This shows that in the context of an 800–1000 mg/d dietary phosphorus restriction (75), on average over 10% of recommended intake could be coming from medications alone. This knowledge could potentially lead to changes in prescribing practices or formulations to reduce phosphate content, but the impact will need to be further evaluated.

In 2009, Sullivan et al. (76) published results from a randomized controlled trial aimed at reducing intake of phosphate additives. Two-hundred seventy-nine patients at 14 hemodialysis centers who had serum phosphate ≥ 5.5 mg/dL were randomized by shift to receive either usual care plus diet education on how to avoid phosphate additives while grocery shopping or at fast food restaurants or usual care alone. At the end of the three month intervention, patients in the diet intervention group had significantly greater decline (by 0.6 mg/dL) in serum phosphate compared with the usual care control group. There is now an additional study (77) newly published in 2017 that supports the conclusions of Sullivan. de Fornasari et al. (77) conducted a similar study in 134 hemodialysis patients at a single dialysis center who had serum phosphate ≥ 5.5 mg/dL were randomized to receive a similar educational intervention to avoid phosphate additives for three months, or usual care. Results showed that a significantly greater proportion of the intervention group achieved serum phosphate ≤ 5.5 mg/dL (69.7% of patients) compared with only 18.5% of control patients at the end of the three month study. The average reduction in serum phosphate was 1.8 mg/dL greater in the intervention group compared with the control group. Furthermore,

this reduction in serum phosphate with the intervention occurred while indices of nutritional status including serum albumin, normalized protein nitrogen appearance, body mass index, tricep skin fold thickness, and arm muscle area remained unchanged and no different between intervention and control at the end of the study. The results of these studies are encouraging, and should be followed with longer term studies to evaluate the effects of limiting phosphate additives, alone or in combination therapy, on improvement of CKD-MBD outcomes including fractures, cardiovascular disease, and mortality.

Conclusions

Phosphorus is widespread in our food supply as both natural organic forms and in added inorganic forms, and humans have a high efficiency for dietary phosphorus absorption. Therefore, phosphorus deficiencies are rare and most people easily meet the RDAs of 700 mg/d for most adults and 1250 mg/d during adolescent growth. Instead, excess dietary phosphorus intake is observed in nearly all age groups in the U.S. Adverse effects of high dietary phosphorus on bone health have been observed in bone animal and human studies, mediated through elevated PTH and increased OPN. The impact of high dietary phosphorus intakes on bone health appears to be compounded by prevalent low calcium intakes in the U.S. However, the case for an optimal Ca:P ratio independent of the absolute values of each nutrient is relatively weak. Further research is needed on the effectiveness of lowering dietary phosphorus intake on fracture risk. However, based on current evidence, a prudent approach would be to limit intake of phosphate additives. Phosphorus from plant based sources remain less bioavailable than animal sources and animal sources less bioavailable compared to inorganic phosphate additives. Additionally, phosphate additives are unrelated to foods' protein content, unlike most naturally-occurring phosphorus in food. So, limiting consumption of inorganic phosphate additives is a strategic way to decrease phosphorus intake without affecting protein intake (77), which is particularly important for patients with CKD on dialysis. At minimum, inclusion of phosphorus content on food labels, and the quantification of phosphorus from inorganic phosphate food additives would be helpful for those seeking to limit their phosphorus intake (4, 7, 15, 17, 63, 78–80).

Acknowledgments

Kathleen Hill Gallant and Ranjani Moorthi report grants from the NIH (NIDDK K01 DK102864), during the conduct of the study.

References

Papers of particular interest, published recently, have been highlighted as:

•Of importance

••Of major importance

1. Institute of Medicine DRI. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press; 1997.
2. Aloia JF, Vaswani A, Yeh JK, Ellis K, Cohn SH. Total body phosphorus in postmenopausal women. Miner Electrolyte Metab. 1984; 10(2):73–6. [PubMed: 6700565]

3. Imel EA, Peacock M. X-linked hypophosphatemia: Understanding and managment. Drugs Future. 2010; 35(9):755–63.

4. Calvo MS, Moshfegh AJ, Tucker KL. Assessing the health impact of phosphorus in the food supply: issues and considerations. Adv Nutr. 2014; 5(1):104–13. [PubMed: 24425729]

5•. McClure ST, Chang AR, Selvin E, Rebholz CM, Appel LJ. Dietary Sources of Phosphorus among Adults in the United States: Results from NHANES 2001–2014. Nutrients. 2017; 9(2) Recent NHANES analysis of relative contributions of various dietary sources of phosphorus to total phosphorus intake in the U.S.

6. Calvo MS, Park YK. Changing phosphorus content of the U.S. diet: potential for adverse effects on bone. J Nutr. 1996; 126(4 Suppl):1168S–80S. [PubMed: 8642452]

7. Calvo MS, Tucker KL. Is phosphorus intake that exceeds dietary requirements a risk factor in bone health? Ann N Y Acad Sci. 2013; 1301:29–35. [PubMed: 24472074]

8. Tucker KL, Morita K, Qiao N, Hannan MT, Cupples LA, Kiel DP. Colas, but not other carbonated beverages, are associated with low bone mineral density in older women: The Framingham Osteoporosis Study. Am J Clin Nutr. 2006; 84(4):936–42. [PubMed: 17023723]

9. Amato D, Maravilla A, Montoya C, Gaja O, Revilla C, Guerra R, et al. Acute effects of soft drink intake on calcium and phosphate metabolism in immature and adult rats. Rev Invest Clin. 1998; 50(3):185–9. [PubMed: 9763881]

10. Garcia-Contreras F, Paniagua R, Avila-Diaz M, Cabrera-Munoz L, Martinez-Muniz I, Foyo-Niembro E, et al. Cola beverage consumption induces bone mineralization reduction in ovariectomized rats. Arch Med Res. 2000; 31(4):360–5. [PubMed: 11068076]

11. Kim SH, Morton DJ, Barrett-Connor EL. Carbonated beverage consumption and bone mineral density among older women: the Rancho Bernardo Study. Am J Public Health. 1997; 87(2):276–9. [PubMed: 9103110]

12. Kristensen M, Jensen M, Kudsk J, Henriksen M, Molgaard C. Short-term effects on bone turnover of replacing milk with cola beverages: a 10-day interventional study in young men. Osteoporos Int. 2005; 16(12):1803–8. [PubMed: 15886860]

13. Wyshak G. Teenaged girls, carbonated beverage consumption, and bone fractures. Arch Pediatr Adolesc Med. 2000; 154(6):610–3. [PubMed: 10850510]

14. Wyshak G, Frisch RE. Carbonated beverages, dietary calcium, the dietary calcium/phosphorus ratio, and bone fractures in girls and boys. J Adolesc Health. 1994; 15(3):210–5. [PubMed: 8075091]

15. Hill Gallant KM. Studying dietary phosphorus intake: the challenge of when a gram is not a gram. Am J Clin Nutr. 2015; 102(2):237–8. [PubMed: 26156742]

16••. Scanni R, vonRotz M, Jehle S, Hulter HN, Krapf R. The human response to acute enteral and parenteral phosphate loads. J Am Soc Nephrol. 2014; 25(12):2730–9. This study used nasoduodenal and intravenous infusions of phosphate and urine phosphorus recovery to show that the kidney completely compensates for added phosphate loads by increasing phosphaturia, and that there appears to be no role for the intestine in regulating renal phosphate excretion in response to a phosphate load. [PubMed: 24854273]

17•. St-Jules DE, Jagannathan R, Gutekunst L, Kalantar-Zadeh K, Sevick MA. Examining the Proportion of Dietary Phosphorus From Plants, Animals, and Food Additives Excreted in Urine. J Ren Nutr. 2017; 27(2):78–83. A recent review article aimed at describing the bioavailablity of phosphorus from plant, animal, and inorganic phosphate additive sources. The authors examine the proportion of dietary phosphorus consumed in four controlled feeding studies that is excreted in the urine as an indirect measure of intestinal phosphorus absorption. This paper illustrates clearly that there is a difference between “digestibility” (i.e. bioaccessibility) of phosphorus from various sources that has been shown through in vitro digestion studies, and the actual bioavailability (absorption) of phosphorus from these foods. [PubMed: 27810171]

18. Bergwitz C, Juppner H. Regulation of phosphate homeostasis by PTH, vitamin D, and FGF23. Annu Rev Med. 2010; 61:91–104. [PubMed: 20059333]

19. Kido S, Kaneko I, Tatsumi S, Segawa H, Miyamoto K. Vitamin D and type II sodium-dependent phosphate cotransporters. Contrib Nephrol. 2013; 180:86–97. [PubMed: 23652552]

20. Forster IC, Hernando N, Biber J, Murer H. Phosphate transporters of the SLC20 and SLC34 families. Mol Aspects Med. 2013; 34(2–3):386–95. [PubMed: 23506879]
21. Fleet, JC., Peacock, M. Physiology of Vitamin D, Calcium, and Phosphate Absorption. In: Morris, HA.Anderson, PH., Nordin, BEC., editors. The Physiological Basis of Metabolic Bone Disease. Boca Raton, FL: CRC Press; 2014. p. 13-40.
22. Miyamoto K, Ito M, Kuwahata M, Kato S, Segawa H. Inhibition of intestinal sodium-dependent inorganic phosphate transport by fibroblast growth factor 23. Ther Apher Dial. 2005; 9(4):331–5. [PubMed: 16076377]
23. Yoshida T, Yoshida N, Monkawa T, Hayashi M, Saruta T. Dietary phosphorus deprivation induces 25-hydroxyvitamin D(3) 1alpha-hydroxylase gene expression. Endocrinology. 2001; 142(5):1720–6. [PubMed: 11316734]
24. Capuano PRT, Wagner CA, Bacic D, Kato S, Uchiyama Y, St-Arnoud R, Murer H, Biber J. Intestinal and renal adaptation to a low-Pi diet of type II NaPi cotransporters in vitamin D receptor- and 1alphaOHase-deficient mice. Am J Physiol Cell Physiol. 2005; 288:C429–C34. [PubMed: 15643054]
25. Segawa H, Kaneko I, Yamanaka S, Ito M, Kuwahata M, Inoue Y, et al. Intestinal Na-P(i) cotransporter adaptation to dietary P(i) content in vitamin D receptor null mice. Am J Physiol-Renal. 2004; 287(1):F39–47.
26. Bonjour JP, Caverzasio J. Phosphate transport in the kidney. Rev Physiol Biochem Pharmacol. 1984; 100:161–214. [PubMed: 6330857]
27. Berndt T, Kumar R. Novel mechanisms in the regulation of phosphorus homeostasis. Physiology (Bethesda). 2009; 24:17–25. [PubMed: 19196648]
28. Shah B, Krishnarao G, Draper H. The relationship of Ca and P nutrition during adult life and osteoporosis in aged mice. J Nutr. 1967; 92:30–42. [PubMed: 6028302]
29. Anderson G, Draper H. Effect of dietary phosphorus on calcium metabolism in intact and parathyroidectomized adult rats. J Nutr. 1972; 102(9):1123–32. [PubMed: 5057198]
30. Draper H, Sie T-L, Bergan J. Osteoporosis in aging rats induced by high phosphorus diets. J Nutr. 1972; 102(9):1133–41. [PubMed: 5057199]
31. Krishnarao G, Draper H. Influence of dietary phosphate on bone resorption in senescent mice. J Nutr. 1972; 102(9):1143–5. [PubMed: 5057200]
32. Koyama Y, Rittling SR, Tsuji K, Hino K, Salincarnboriboon R, Yano T, et al. Osteopontin deficiency suppresses high phosphate load-induced bone loss via specific modulation of osteoclasts. Endocrinology. 2006; 147(6):3040–9. [PubMed: 16513836]
33. Huttunen MM, Tillman I, Viljakainen HT, Tuukkanen J, Peng Z, Pekkinen M, et al. High dietary phosphate intake reduces bone strength in the growing rat skeleton. J Bone Miner Res. 2007; 22(1):83–92. [PubMed: 17042736]
34. Antoniucci DM, Yamashita T, Portale AA. Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. J Clin Endocrinol Metab. 2006; 91(8):3144–9. [PubMed: 16735491]
35. Brixen K, Nielsen HK, Charles P, Mosekilde L. Effects of a short course of oral phosphate treatment on serum parathyroid hormone (1–84) and biochemical markers of bone turnover: a dose-response study. Calcified Tissue Int. 1992; 51(4):276–81.
36. Burnett SM, Gunawardene SC, Bringhurst FR, Juppner H, Lee H, Finkelstein JS. Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. J Bone Miner Res. 2006; 21(8):1187–96. [PubMed: 16869716]
37. Calvo MS, Kumar R, Heath H 3rd. Elevated secretion and action of serum parathyroid hormone in young adults consuming high phosphorus, low calcium diets assembled from common foods. J Clin Endocrinol Metab. 1988; 66(4):823–9. [PubMed: 2831248]
38. Calvo MS, Kumar R, HEATH H III. Persistently elevated parathyroid hormone secretion and action in young women after four weeks of ingesting high phosphorus, low calcium diets. J Clin Endocrinol Metab. 1990; 70(5):1334–40. [PubMed: 2335575]
39. Grimm M, Muller A, Hein G, Funfstuck R, Jahreis G. High phosphorus intake only slightly affects serum minerals, urinary pyridinium crosslinks and renal function in young women. Eur J Clin Nutr. 2001; 55(3):153. [PubMed: 11305263]

40. Kärkkäinen M, Lamberg-Allardt C. An acute intake of phosphate increases parathyroid hormone secretion and inhibits bone formation in young women. J Bone Miner Res. 1996; 11(12):1905–12. [PubMed: 8970892]
41. Karp HJ, Vaihia KP, Karkkainen MU, Niemisto MJ, Lamberg-Allardt CJ. Acute effects of different phosphorus sources on calcium and bone metabolism in young women: a whole-foods approach. Calcified Tissue Int. 2007; 80(4):251–8.
42. Kemi VE, Kärkkäinen MU, Lamberg-Allardt CJ. High phosphorus intakes acutely and negatively affect Ca and bone metabolism in a dose-dependent manner in healthy young females. Br J Nutr. 2006; 96(03):545–52. [PubMed: 16925861]
43. Silverberg SJ, Shane E, Clemens TL, Dempster DW, Segre GV, Lindsay R, et al. The effect of oral phosphate administration on major indices of skeletal metabolism in normal subjects. J Bone Mineral Res. 1986; 1(4):383–8.
44. Whybro A, Jagger H, Barker M, Eastell R. Phosphate supplementation in young men: lack of effect on calcium homeostasis and bone turnover. Eu J Clin Nutr. 1998; 52(1):29–33.
45. Reiss E, Canterbury JM, Bercovitz MA, Kaplan EL. The role of phosphate in the secretion of parathyroid hormone in man. J Clin Invest. 1970; 49(11):2146–9. [PubMed: 5475987]
46. Calvo MS, Heath H 3rd. Acute effects of oral phosphate-salt ingestion on serum phosphorus, serum ionized calcium, and parathyroid hormone in young adults. Am J Clin Nutr. 1988; 47(6): 1025–9. [PubMed: 2837078]
47. Ferrari SL, Bonjour JP, Rizzoli R. Fibroblast growth factor-23 relationship to dietary phosphate and renal phosphate handling in healthy young men. J Clin Endocrinol Metab. 2005; 90(3):1519–24. [PubMed: 15613425]
48. Vervloet MG, van Ittersum FJ, Buttler RM, Heijboer AC, Blankenstein MA, ter Wee PM. Effects of dietary phosphate and calcium intake on fibroblast growth factor-23. Clin J Am Soc Nephrol. 2011; 6(2):383–9. [PubMed: 21030580]
49. Lee AW, Cho SS. Association between phosphorus intake and bone health in the NHANES population. Nutr J. 2015; 14(1):28. [PubMed: 25856461]
50. Lee K-J, Kim K-S, Kim H-N, Seo J-A, Song S-W. Association between dietary calcium and phosphorus intakes, dietary calcium/phosphorus ratio and bone mass in the Korean population. Nutr J. 2014; 13(1):114. [PubMed: 25496564]
51. Brot C, Jørgensen N, Madsen O, Jensen L, Sørensen O. Relationships between bone mineral density, serum vitamin D metabolites and calcium: phosphorus intake in healthy perimenopausal women. J Intern Med. 1999; 245(5):509–16. [PubMed: 10363752]
52. Pinheiro MM, Schuch NJ, Genaro PS, Ciconelli RM, Ferraz MB, Martini LA. Nutrient intakes related to osteoporotic fractures in men and women–The Brazilian Osteoporosis Study (BRAZOS). Nutr J. 2009; 8(1):6. [PubMed: 19178745]
53••. Campos-Obando N, Koek WN, Hooker ER, van der Eerden BC, Pols HA, Hofman A, et al. Serum Phosphate Is Associated With Fracture Risk: The Rotterdam Study and MrOS. J Bone Miner Res. 2017 Serum phosphate levels within the normal range are associated with an increased fracture risk in men and women from the Rotterdam Study and men from MrOS. This was independent of phosphorus intake, but the authors note that phosphate intake accuracy may be limited by assessment methods.
54. Katsumata S, Matsuzaki H, Katsumata-Tsuboi R, Uehara M, Suzuki K. Effects of high phosphorus diet on bone metabolism-related gene expression in young and aged mice. J Nutr Metab. 2014; 2014
55. Katsumata S, Matsuzaki H, Uehara M, Suzuki K. Effects of Dietary Calcium Supplementation on Bone Metabolism, Kidney Mineral Concentrations, and Kidney Function in Rats Fed a High-Phosphorus Diet. J Nutr Sci Vitaminol. 2015; 61(2):195–200. [PubMed: 26052152]
56. Heaney RP, Recker RR. Effects of nitrogen, phosphorus, and caffeine on calcium balance in women. J Lab Clin Med. 1982; 99(1):46–55. [PubMed: 7054349]
57. Spencer H, Kramer L, Osis D, Norris C. Effect of phosphorus on the absorption of calcium and on the calcium balance in man. J Nutr. 1978; 108(3):447–57. [PubMed: 627919]
58. Spencer H, Menczel J, Lewin I, Samachson J. Effect of High Phosphorus Intake on Calcium and Phosphorus Metabolism in Man. J Nutr. 1965; 86:125–32. [PubMed: 14300991]

59. Teegarden D, Lyle RM, McCabe GP, McCabe LD, Proulx WR, Michon K, et al. Dietary calcium, protein, and phosphorus are related to bone mineral density and content in young women. Am J Clin Nutr. 1998; 68(3):749–54. [PubMed: 9734757]

60. Sax L. The institute of medicine's "dietary reference intake" for phosphorus: a critical perspective. J Am Coll Nutr. 2001; 20(4):271–8. [PubMed: 11506054]

61. Kemi VE, Karkkainen MU, Rita HJ, Laaksonen MM, Outila TA, Lamberg-Allardt CJ. Low calcium:phosphorus ratio in habitual diets affects serum parathyroid hormone concentration and calcium metabolism in healthy women with adequate calcium intake. Br J Nutr. 2010; 103(4):561–8. [PubMed: 19781123]

62. Carrigan A, Klinger A, Choquette SS, Luzuriaga-McPherson A, Bell EK, Darnell B, et al. Contribution of food additives to sodium and phosphorus content of diets rich in processed foods. J Ren Nutr. 2014; 24(1):13–9. 9e1. [PubMed: 24355818]

63. Calvo MS, Uribarri J. Contributions to total phosphorus intake: all sources considered. Semin Dial. 2013; 26(1):54–61. [PubMed: 23278245]

64. McGartland C, Robson PJ, Murray L, Cran G, Savage MJ, Watkins D, et al. Carbonated soft drink consumption and bone mineral density in adolescence: the Northern Ireland Young Hearts project. J Bone Miner Res. 2003; 18(9):1563–9. [PubMed: 12968664]

65••. Gutiérrez OM, Luzuriaga-McPherson A, Lin Y, Gilbert LC, Ha S-W, Beck GR Jr. Impact of phosphorus-based food additives on bone and mineral metabolism. J Clin Endocrinol Metab. 2015; 100(11):4264–71. This is a controlled feeding study that shows the adverse effects of increasing dietary phosphorus through addition of inorganic phosphate additives on bone metabolism in healthy adults. The authors also present complementary studies in mice that show similar adverse effects on bone and mineral metabolism, including detrimental effects of phosphate additives on bone mineral density and cortical and cancellous bone geometry. [PubMed: 26323022]

66. Bell RR, Draper HH, Tzeng DY, Shin HK, Schmidt GR. Physiological responses of human adults to foods containing phosphate additives. J Nutr. 1977; 107(1):42–50. [PubMed: 189000]

67. Zemel MB, Linkswiler HM. Calcium metabolism in the young adult male as affected by level and form of phosphorus intake and level of calcium intake. J Nutr. 1981; 111(2):315–24. [PubMed: 6257868]

68. Kuntz D, Marie P, Berhel M, Caulin F. Treatment of post-menopausal osteoporosis with phosphate and intermittent calcitonin. Int J Clin Pharmacol Res. 1986; 6(2):157–62. [PubMed: 3522444]

69. Kemi VE, Karkkainen MU, Karp HJ, Laitinen KA, Lamberg-Allardt CJ. Increased calcium intake does not completely counteract the effects of increased phosphorus intake on bone: an acute dose-response study in healthy females. Br J Nutr. 2008; 99(4):832–9. [PubMed: 17903344]

70. Sigrist M, Tang M, Beaulieu M, Espino-Hernandez G, Er L, Djurdjev O, et al. Responsiveness of FGF-23 and mineral metabolism to altered dietary phosphate intake in chronic kidney disease (CKD): results of a randomized trial. Nephrol Dial Transplant. 2013; 28(1):161–9. [PubMed: 23024219]

71. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006; 69(11):1945–53. [PubMed: 16641930]

72. Moorthi RN, Moe SM. Recent advances in the noninvasive diagnosis of renal osteodystrophy. Kidney Int. 2013; 84(5):886–94. [PubMed: 23802194]

73. Kalantar-Zadeh K, Tortorici AR, Chen JL, Kamgar M, Lau WL, Moradi H, et al. Dietary restrictions in dialysis patients: is there anything left to eat? Semin Dial. 2015; 28(2):159–68. [PubMed: 25649719]

74•. Nelson SM, Sarabia SR, Christilaw E, Ward EC, Lynch SK, Adams MA, et al. Phosphate-Containing Prescription Medications Contribute to the Daily Phosphate Intake in a Third of Hemodialysis Patients. J Ren Nutr. 2017; 27(2):91–6. This is an analysis of the phosphorus content of medications used by hemodialysis patients, showing that medications can contribute a meaningful amount of phosphorus to total intake for patients who are often advised to follow a phosphorus-restricted diet. [PubMed: 27814946]

75. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003; 42(4 Suppl 3):S1–201. [PubMed: 14520607]

76. Sullivan C, Sayre SS, Leon JB, Machekano R, Love TE, Porter D, et al. Effect of food additives on hyperphosphatemia among patients with end-stage renal disease: a randomized controlled trial. J Am Med Assoc. 2009; 301(6):629–35.

77••. de Fornasari ML, Dos Santos Sens YA. Replacing Phosphorus-Containing Food Additives With Foods Without Additives Reduces Phosphatemia in End-Stage Renal Disease Patients: A Randomized Clinical Trial. J Ren Nutr. 2017; 27(2):97–105. This is a 3-month randomized controlled trial of an educational intervention to decreased phosphate additive intake in hemodialysis patients that corroborates the work of Sullivan et al. (2009). Patients who received the intervention had significantly improved serum phosphate after three months, with no change in indicators of nutritional status. [PubMed: 27751628]

78. Takeda E, Yamamoto H, Yamanaka-Okumura H, Taketani Y. Dietary phosphorus in bone health and quality of life. Nutr Rev. 2012; 70(6):311–21. [PubMed: 22646125]

79. Sehgal AR, Sullivan C, Leon JB, Bialostosky K. Public health approach to addressing hyperphosphatemia among dialysis patients. J Ren Nutr. 2008; 18(3):256–61. [PubMed: 18410881]

80. Karalis M. Food and Drug Administration petition on food labeling: an update from the American Dietetic Association and National Kidney Foundation. J Ren Nutr. 2007; 17(6):423–4. [PubMed: 17971315]

Table 1

Effects of high phosphorus dietary interventions on bone metabolism in human subjects

Study Characteristics							Effects of higher dietary P			
Ref	**Subject Description**	**Phosphorus Form**	**P intake level(s), mg/d**	**Ca intake level(s), mg/d**	**Ca:P mass ratio(s)**	**Intervention Length**	**Resorption Markers**	**Formation Markers***	**Serum P & Ca**	**PTH**
Reiss et al. (1970) (45)	5 men and women, 23–46 y	Sodium phosphate	+ 1000$_{(\text{to baseline})}$	unknown	unknown	2 hours			↔ P ↓ Ca, iCa	↑
Bell et al. (1977) (66)	8 men and women, 24–36 y	Additive substitutions from food	979 2124	~ 700 ~ 700	0.7 0.33	4 weeks	↑ hydroxyproline		↑ P ↓ Ca	N/A
Zemel & Linkswiler (1981) (67)	8 men, 18–24 y	Monobasic potassium phosphate (MP), polyphosphate (PP), sodium hexametaphosphate (SH), or orthophosphate (O)	Baseline: 835 +1000 (to baseline as O) +1000 as SH +1000 as MP)	399 399 399 +800	0.48 0.22 0.22 0.65	15 days	↔ hydroxyproline			
Kuntz et al. (1986) (68)	19 postmenopausal women with vertebral osteopenia	Glycerol phosphate/magnesium phosphate monobasic	+ 0$_{(\text{to baseline})}$ + 1500			6 months	↔ hydroxyproline Histomorphometry ↔ osteoclastic resorption surface	Histomorpho metry ↑ osteoblastic surface ↔ trabecular bone volume	↔ P ↔ Ca	↔
Silverberg et al. (1986) (43)	13 men and women, 19–36 y	Unknown supplement	+ 2000$_{(\text{to baseline})}$	unknown	unknown	5 days	↔ hydroxyproline	↑ osteocalcin	↑ P ↓ Ca	↑
Calvo et al. (1988) (37)	9 men and women, 18–25 y	Substitutions from food	~ 1600 ~ 800	~ 400 ~ 800	0.25 1.0	24 hours	↑ hydroxyproline		↑ P ↔ Ca, iCa (men) ↓ Ca, iCa (women)	↑
Calvo et al (1988) (46)	16 men and women, 18–25 y	Sodium-potassium phosphate	+ 1000$_{(\text{to baseline})}$ + 1500	unknown	unknown	5 hours			↑ P (both) ↔ iCa (both)	↔ (w/1g P) ↑ (w/1.5g P)
Calvo et al. (1990) (38)	15 women, 18–25 y	Additive substitutions from food	~ 900 ~ 1700	~ 800 ~ 400	0.9 0.24	4 weeks	↔ hydroxyproline	↔ ALP ↔ osteocalcin	↔ P ↓ iCa	↑
Brixen et al. (1992) (35)	79 women, 50–75 y, history of fracture	Ammonium phosphate/potassium phosphate/glycerol phosphate	+ 0$_{(\text{to baseline})}$ + 750 + 1500 + 2550	unknown	unknown	7 days (follow-up until 4 months)	↔ hydroxyproline	↔ osteocalcin ↔ BALP	↔ P ↔ Ca	↑
Kärkkäinen and Lamberg-Allardt (1996) (40)	20 women, 21–34 y	Sodium phosphate	878 2378	375 375	0.43 0.16	24 hours	↔ ICTP ↔ DPD	↓ PICP (single dose) ↔ PICP (3 doses spread out) ↔ osteocalcin ↓ BALP	↑ P ↓ Ca (single dose)	↑
Whybro et al. (1998) (44)	22 men, 19–38 y	Sodium acid phosphate/sodium bicarbonate/pot assium bicarbonate	Exp1: ~800, 1800	Exp1: ~800 Exp2: ~1000	Exp 1: 1.0, 0.44	1 week	↔ DPD (Exp 2) ↔ NTX (Exp 1)	↔ osteocalcin (Exp 1)	↔ P ↔ Ca	↑ (Exp 1)

Study Characteristics							Effects of higher dietary P			
Ref	**Subject Description**	**Phosphorus Form**	**P intake level(s), mg/d**	**Ca intake level(s), mg/d**	**Ca:P mass ratio(s)**	**Intervention Length**	**Resorption Markers**	**Formation Markers***	**Serum P & Ca**	**PTH**
			Exp2: ~1000, 2000, 2500, 3000		Exp 2: 1.0, 0.5, 0.4, 0.33					↔ (Exp 2, highest vs lowest P)
Grimm et al. (2001) (39)	10 women, 23–29 y	Sodium polyphosphates	1700 3008	1500 1995	0.88 0.66	4 weeks	↔ DPD ↔ PYD	↔ osteocalcin	↔ P ↔ Ca	↑
Ferrari et al. (2005) (47)	29 men, 20.7–38.6 y	Potassium-phosphorus syrup	540 2860	590 1660	1.09 0.58	5 days			↔ P ↔ Ca, iCa	↔ (also higher Ca)
Burnett et al. (2006) (36)	66 men and women, 28±8 and 26±7 y	Sodium and potassium phosphate	500 (+ P binders) 2500	1000 1000	2.0 0.4	4 days			↔ P ↔ Ca	↑
Antoniucci et al. (2006) (34)	13 men, 28–43 y	Sodium and potassium phosphate	625 2300	850 850	1.36 0.40	9 days			↔ P ↔ Ca	↑
Kemi et al. (2006) (42)	14 women, 20–28 y	Disodium and trisodium phosphate	495 745 1245 1995	990 990 990 990	0.51 0.34 0.20 0.13	4 weeks	↑ NTX	↓ BALP	↑ P ↓ iCa (highest dose)	↑
Karp et al. (2007) (41)	16 women, 20–30 y	Meat, cheese, whole grains	484 (control) 1435 (meat) 1509 (whole grains) 1624 (cheese) 1458 (supplement)	235 274 352 2044 246	0.49 0.19 0.23 1.26 0.17	24 hours	↑ NTX (meat, whole grain), ↓ (cheese)	↔ BALP	↑ P (all vs control) ↑ iCa (cheese), ↓ supplement	↓ (w/cheese) ↑ (w/supplement)
Kemi et al. (2008) (69)	12 women, 21–40 y	Calcium carbonate	1850 1850 1850	480 1080 1680	0.26 0.58 0.91	24 hours	↑ NTX (with lower Ca:P)	↔ BALP	↔ P ↓ iCa (with lower Ca:P) ↔ Ca	↑ (with lower Ca:P)
Vervloet et al. (2011) (48)	10 men and women, 23.5±1.6 y	Substitutions from food	850 2880	280 1700	0.33 0.59	36 hours			↑ P	↓ (also high Ca)
Sigrist et al. (2013) (70)	30 men and women Healthy: 31–48 y CKD: 57–77 y	Substitutions from food	750 (+ P binder) 750 2000	unknown	unknown	7 days			↑ P ↔ Ca	↔
Gutiérrez et al. (2015) (65)	10 men and women, 31±9 y	Additive substitutions from food	~ 1000 ~ 1600	~ 700 ~ 700	0.7 0.44	1 week	↔ CTX Also: ↑ osteopontin	↓ P1NP (p = 0.06) ↑ osteocalcin Also: ↓ sclerostin	↔ P ↔ Ca	↔

*osteocalcin is included in the formation marker column, but is generally considered a marker of overall bone turnover, rather than specific to formation.