Lead Article

Dietary phosphorus in bone health and quality of life

Eiji Takeda, Hironori Yamamoto, Hisami Yamanaka-Okumura, and Yutaka Taketani

Awareness of phosphorus intake is important because both phosphorus deficiency and overloading impair bone health and quality of life. Phosphorus consumption is increasing in many countries. Most dietary phosphorus is contained in protein-rich foods such as meat, milk, cheese, poultry, fish, and processed foods that contain phosphate-based additives to improve their consistency and appearance. Elevation of extracellular phosphorus levels causes endothelial dysfunction and medial calcification, which are closely associated with the development of cardiovascular disease (CVD). Long-term excessive phosphorus loading, even if it does not cause hyperphosphatemia, can be a risk factor for CVD. In epidemiological studies, higher levels of phosphorus intake have been associated with reduced blood pressure. Interestingly, when examined further, phosphorus from dairy products, but not from other sources, was usually associated with lower blood pressure. A dietary approach to phosphorus reduction is particularly important to prevent bone impairment and CVD in patients with chronic kidney disease. In order to improve bone health and quality of life in the general population, the impact of phosphorous, including in processed foods, should be considered, and measures to indicate the amount of phosphorous in food products should be implemented.

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INTRODUCTION

Phosphorus is an essential nutrient in the processes of glycolysis, gluconeogenesis, energy metabolism, skeletal mineralization, and cellular signal transduction in every cell of the body. Although more than 80% of total body phosphorus is stored in the bones and teeth, intracellular phosphorus exists in the form of organic compounds such as adenosine triphosphate and as free anions like H_2PO_4, which are commonly referred to as phosphate. Serum phosphorus is primarily in the form of inorganic phosphate, which is maintained within the physiological range by regulation of dietary absorption, bone formation, and renal excretion, as well as equilibration with intracellular stores.[1–4] Phosphorus is a critical component of virtually all enzymes, cellular messengers such as the G-proteins, and carbohydrate fuels. Certain hormones depend upon phosphorylation for their activation. Phosphorus is also of vital importance for acid-base regulation.

Acute dietary phosphorus deprivation results in skeletal demineralization even before the serum phosphorus concentration falls. When the amount of phosphorus in serum is modestly depressed, calcium may be low or normal and alkaline phosphatase activity is usually elevated. Rickets or osteomalacia, defined as a defect in bone mineralization, often occurs in individuals with long-standing phosphorus deficiency. Chronic phosphorus deficiency in humans causes proximal myopathy.[5] Proximal muscle atrophy and weakness may be striking. Furthermore, acute hypophosphatemia may precipitate rhabdomyolysis if it occurs in conjunction with chronic phosphorus depletion.[6,7] Plasma phosphorus concentration regulates erythrocyte synthesis and stores of 2,3-diphosphoglycerate (2,3-DPG), which is bound to hemoglobin. This substance plays an important role in the affinity of hemoglobin for oxygen. When 2,3-DPG is elevated, as it is in children, hemoglobin releases its oxygen more easily; as a result, blood hemoglobin

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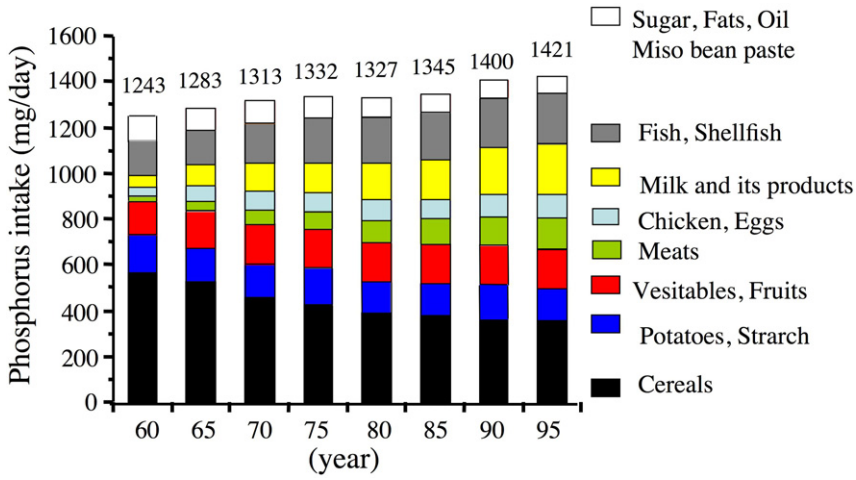

Figure 1 **The amounts of phosphorus intake from food in Japan.** Reproduced from Takeda E et al. (2002)[15] with permission.

concentration and hematocrit are set at lower values. Symptoms of nervous system dysfunction, such as weakness, apathy, a bedridden state, and intention tremors, are observed in severe hypophosphatemia.[8]

It is possible that higher levels of circulating serum phosphorus reflect increased bone resorption and osteoporosis, which is associated with vascular calcification.[9] Higher levels of serum phosphorus within the normal range are associated with increased calcification of the coronary arteries, the mitral and aortic valves, and the thoracic aorta among people with a glomerular filtration rate of 60 mL/min 1.73 m^2, but it is not associated with kidney failure.[10] Thus, recent attention has focused on the independent association between serum levels of phosphorus and the risk of death and other adverse clinical outcomes among people with apparently normal kidney function or with only moderate chronic kidney disease (CKD).[11–14] In light of all these factors, awareness of phosphorus intake is important because both phosphorus deficiency and overloading impair bone health and quality of life.

LEVELS OF PHOSPHORUS INTAKE

In Japan, the amounts of phosphorus available for consumption, as calculated from the national Food Balance Sheet, increased gradually from 1,243 mg/day in 1960, to 1,332 mg/day in 1975, to 1,421 mg/day in 1995 (Figure 1).[15] These increases can be explained by rising consumption of cow's milk and milk products, meat, and chicken eggs. The main foods supplying phosphorus in 1995 were cereals, milk and milk products, fish and shellfish, and vegetables, with respective contributions of 24.4%, 15.8%, 14.2%, and 10.9%. The phosphorus-to-calcium ratio calculated from the Food Balance Sheet in 1960 was 3.51, but it decreased to 2.89 in 1975 and to 2.44 in 1995.

The increases in the amounts of phosphorus in the food supply in Japan are evident in other countries as well. In the United States, for example, phosphorous intake has increased considerably in recent decades, particularly because of the significant amounts of phosphorus added to processed foods.[16] The average diet in North America and in Europe contains approximately 1,000 to 1,500 mg of phosphorus per day, compared to the recommended intake level of 700 mg/day.[17] Most dietary phosphorus is contained in protein-rich foods such as meat, milk, cheese, poultry, and fish; however, processed foods are also high in phosphorus, with items such as processed meats containing phosphate-based additives to improve the food's consistency and appearance. Between 1990 and 1996, dietary phosphorus intake from food additives doubled in the United States and was reported to have reached 1,000 mg per day in 1996.[16] Beverages such as sodas, juices, and sport drinks also contain phosphorus additives.[18] Thus, total phosphorus intake depends not only on the raw quantities found in "natural" protein sources, but also on the growing amount of phosphorus-rich additives in processed and fast foods as well as in beverages.[19–22] These additives can augment phosphorus intake by as much as 1,000 mg per day, but they are often not captured by standard dietary instruments because the amount of phosphorous in foods and beverages does not presently need to be quantified on product labels.[23,24] Consequently, large gaps may exist between estimated and actual phosphorus intake.[19,21,25]

Poverty is a major public health burden that may promote excess dietary intake of phosphorus. For example, the fact that residents of low-income neighborhoods often have limited access to foods that are healthy

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and affordable results in excessive consumption of inexpensive processed and fast foods that are often rich in highly-absorbable phosphorus additives.[26–29] Poverty is also independently associated with higher serum phosphate levels in patients both with and without CKD.[30,31]

Protein-rich foods and cereal grains are rich sources of phosphorus. Among ten studies included in the European Prospective Investigation in Cancer and Nutrition Study, it was found that, overall, the greatest contributors to phosphorus intake are dairy foods and products, cereals and cereal products, and meats and meat products; in all countries, in both men and women, these foods accounted for between approximately 63% (in Spain) and approximately 75% (in Denmark) of phosphorus intake.[32] In the United States, about half the phosphorus in the diet comes from milk, meat, poultry, and fish, with cereals providing 12%. Among males, alcoholic beverages account for 9.2% of phosphorus intake in Germany, 6.1% in the Netherlands, and 5.0% in Italy. In Germany and the Netherlands, the greatest contributor within the alcoholic beverages group was beer (Germany 5.5%, the Netherlands 3.8%), whereas in Italy it was wine (3.5%). In women, the contribution from alcoholic beverages was <3%.[32] A diet rich in proteins is usually rich in phosphorus. However, proteins with very different phosphorus contents can provide equivalent nutritional value, as can be seen from the difference in phosphorus content between meat, cheese, and eggs. Egg white is an excellent example of food with a high level of protein but low phosphorus content. Moe et al.[33] demonstrated the importance of the protein source of phosphorus in overall mineral metabolism after only 7 days of controlled diets. Despite equivalent protein and phosphorus concentrations in the diets, subjects had lower serum phosphorus levels, a trend toward decreased urine 24-h phosphorus excretion, and significantly decreased fibroblast growth factor (FGF23) levels when they consumed a vegetarian diet compared with a meat-based diet.[33]

PHOSPHATE METABOLISM

The metabolism of phosphate in the body represents a complex interplay between various factors that can affect the digestion, absorption, distribution, and excretion of this element. Phosphate absorption in the renal proximal tubule is important for phosphate homeostasis. This process is a major regulator of phosphate homeostasis and has sufficient reabsorptive capacity for phosphate to accommodate physiologic phosphate requirements. Up to 70% of filtered phosphate is reabsorbed in the proximal tubule where sodium-dependent phosphate transport systems in the brush-border membrane mediate the rate-limiting step in the overall phosphate reabsorptive process.[1,34–37] Three different types of sodium-dependent phosphate transporters have been identified to date; these are types I, II, and III. The sodium-dependent phosphate transport system includes the type IIa and type IIc Na-dependent phosphate cotransporters, which are localized in the apical membrane of renal proximal tubular cells, and the type IIb Na-dependent phosphate cotransporter, which is localized in the apical membrane of intestinal epithelial cells. The type IIa Na-dependent phosphate transporter is the major determinant of plasma phosphate level and urinary phosphate excretion.[1,34–37] This transporter is regulated by physiological stimuli; for example, type IIa transporter levels in the apical membrane are increased in response to dietary restriction of phosphate and 1,25-dihydroxy-vitamin D [1,25$(OH)_2$D] and decreased in response to parathyroid hormone, or a high-phosphate diet. In addition, intestinal phosphate transport activity and type IIb Na-dependent phosphate transporter levels are upregulated by 1,25$(OH)_2$D.[38,39]

Fibroblast growth factor 23 (FGF23), a recently identified member of the FGF family, is involved in renal phosphate homeostasis.[40,41] FGF23 regulates phosphorus and vitamin D metabolism. In healthy individuals, FGF23 is secreted by osteocytes in response to dietary phosphorus loading or an increase in 1,25$(OH)_2$D levels; it stimulates phosphaturia and reduces 1,25$(OH)_2$D and parathyroid hormone levels.[42,43] FGF23 achieves its cellular specificity in the kidney and parathyroid glands by binding in the presence of its obligatory transmembrane protein coreceptor klotho, which increases the affinity of FGF23 for ubiquitously expressed FGF receptors.[44] Oral phosphorus loading and calcitriol stimulate FGF23 secretion while dietary phosphorus restriction inhibits it.[45–48] When a diet rich in phosphorus is consumed, high levels of FGF23 induce phosphaturia and inhibit 1,25$(OH)_2$D production, which decreases the efficiency of dietary phosphorus absorption. On a low-phosphorus diet, low FGF23 levels promote renal phosphate conservation and enhance gut absorption of phosphorus as a result of increased 1,25$(OH)_2$D. This suggests that serum phosphorus levels are regulated within a narrow range by FGF23. However, studies that have evaluated the short-term effects of a low-phosphorus diet or phosphorus supplementation have failed to find changes in FGF23 in healthy individuals after 6 h[49] or 2–3 days.[50] This indicates that FGF23 is not associated with rapid adaptation of phosphate homeostasis. FGF23 levels increase with progressive deterioration in renal function,[50,51] and FGF23 levels at the start of dialysis are highly predictive of mortality.[52] Excessive production of FGF23 by osteocytes is an appropriate compensation to help maintain normal phosphorus metabolism in these patients. Beginning in early CKD, progressive increases in levels of FGF23

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enhance phosphaturia on a per nephron basis and inhibit $1,25(OH)_2D$ production, thereby contributing centrally to the predominant phosphorus phenotype of predialysis kidney disease, normal serum phosphorus, increased fractional excretion of phosphorus, and $1,25(OH)_2D$ deficiency.

Klotho is an important factor for FGF23 function and is an anti-aging factor. Both *Fgf23*$^{-/-}$ and *klotho* mice have been found to exhibit short lifespan and various premature aging-like characteristics, such as arteriosclerosis, ectopic calcification in various soft tissues, osteopenia, emphysema, atrophy of the skin, and severe hyperphosphatemia with increased concentrations of serum $1,25(OH)_2D$.[53–55] These findings may be inferred, however, because a phosphorus restriction diet partially ameliorated the phenotype in both klotho and FGF23-deficient mice.[56,57]

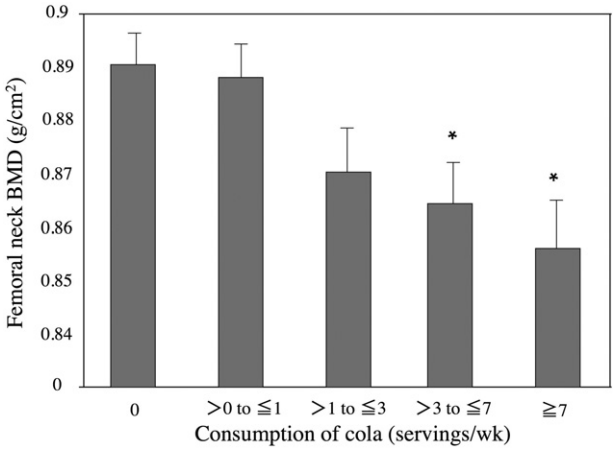

Figure 2 **Femoral neck bone mineral density (BMD) and total cola intake in the women.** Reproduced from Tucker KL et al. (2006)[62] with permission.

PHOSPHORUS AND BONE HEALTH

In physiologically normal adults, phosphorus deprivation causes release of calcium from the skeleton and hypercalciuria. However, hypercalcemia does not occur. Rickets or osteomalacia often occurs in genetic hypophosphatemia and long-standing phosphorus deficiency.

Diets high in phosphorus and low in calcium lead to complexes that reduce serum calcium, stimulating parathyroid hormone (PTH), which, in turn, causes bone resorption and returns serum calcium to homeostatic concentrations. High dietary phosphorus has been shown to cause bone loss in animals.[58] Furthermore, for every 100 mg of phosphorus intake, the risk of fractures increases by 9%. The potential adverse effects of higher phosphorus intake on bone metabolism have been investigated by several authors in recent decades, and it has been demonstrated that a high-phosphorus diet produces hormonal changes equivalent to mild hyperparathyroidism, lowering $1,25(OH)_2D$ concentrations and thus disrupting calcium homeostasis.[16,59,60] These results demonstrated deficiencies in bone-related nutrients in the population as well as showing that an increase in phosphorus intake is related to bone fractures. Higher PTH and hyperphosphaturia have been reported in postmenopausal women with low serum calcium ($\leq$8.8 mg calcium/dL compared with >8.8 mg calcium/dL), and the women with low serum calcium were significantly more likely to consume $\geq$1 cola/day. Cola beverages contain phosphoric acid, which has been shown to interfere with calcium absorption and to contribute to imbalances that lead to additional loss of calcium,[61] whereas other carbonated soft drinks (with some exceptions) do not. In this large population-based cohort, a consistent robust association was observed between cola consumption and low bone mineral density in women (Figure 2).[62] A deleterious effect of phosphoric acid has been proposed.[63] Although cola drinkers did have lower calcium-to-phosphorus intake ratios than noncola drinkers, adjustment for this variable did not significantly attenuate the results and the ratio itself was not significant. While phosphorus is a fundamental mineral component of hydroxyapatite, the principal structural element of bone, the acid-ash hypothesis posits that dietary phosphorus, a marker of the metabolic production of acid, is detrimental to bone.[64–66]

PHOSPHORUS AND VASCULAR HEALTH

Postprandial hyperphosphatemia and vascular health

After ingestion of a meal containing 400 mg of phosphorus and 200 mg of calcium by healthy men, serum phosphorus levels increased at 2 h and were sustained until 6 h after the meal. A meal containing 1,200 mg of phosphorus and 200 mg of calcium also increased serum phosphorus levels at 2 h after ingestion. The peak values exceeded the normal range (between 2.5 and 4.5 mg/dL).[49] Thus, dietary phosphorus loading in humans caused postprandial elevation of serum phosphorus and impaired endothelium-dependent vasodilation; it also demonstrated that the impairment of vasodilation was mainly due to decreased nitric oxide (NO) production in endothelial cells, suggesting this short-term exposure to phosphate was enough to decrease endothelium-dependent vasodilation.[49] Portale et al.[67] demonstrated that the range of circadian variation of serum phosphorus levels in humans was dependent on the amount of dietary phosphorus intake.

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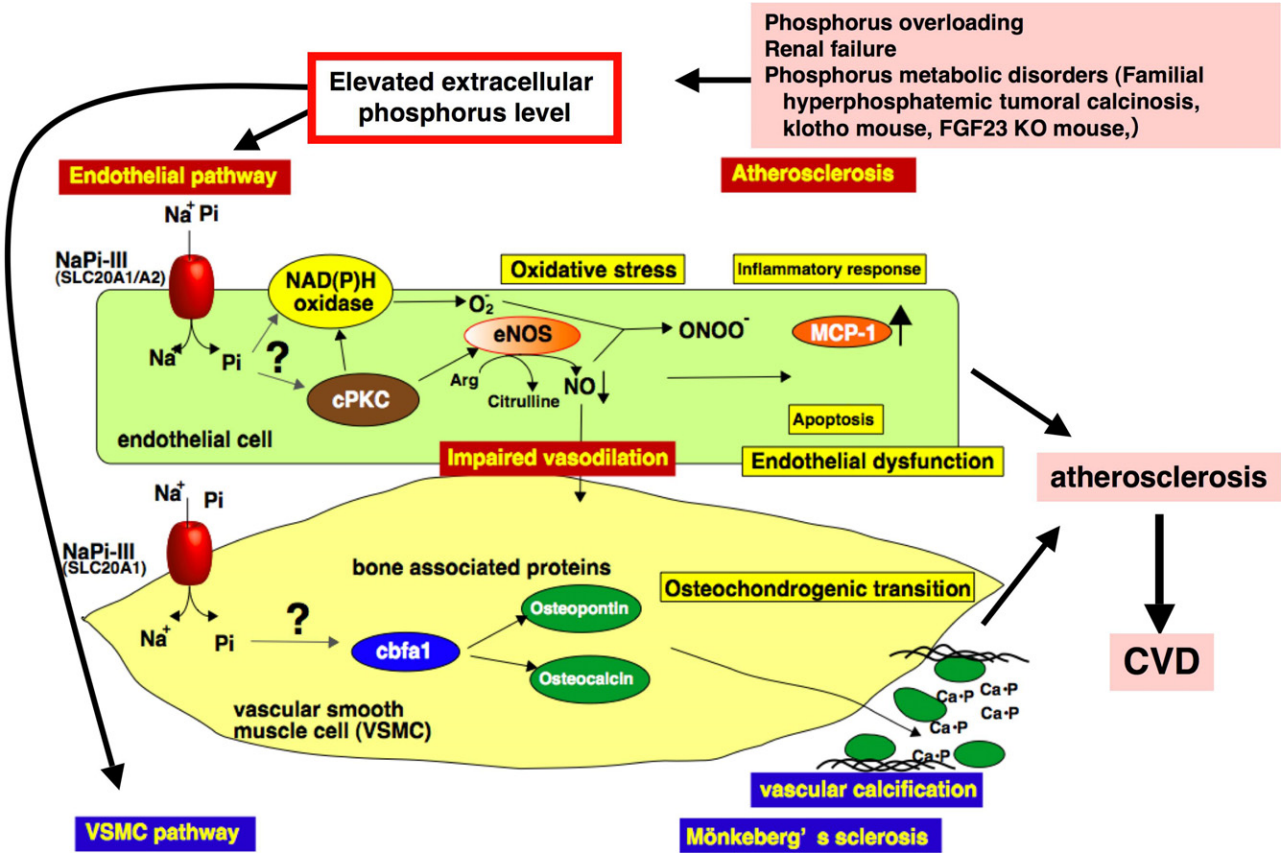

Figure 3 **Hyperphosphatemia increases the risk of cardiovascular disease due to impaired endothelial function and smooth muscle cell calcification.**

Phosphorus and atherosclerosis

Hyperphosphatemia has been recognized as a risk factor for cardiovascular disease (CVD) through promotion of medial calcification.[68–70] Jono et al.[69] demonstrated that phosphorus levels above 1.4 mM dose-dependently increased calcium deposition after a 6-day incubation in human smooth muscle cells. This finding could explain the correlation between hyperphosphatemia in CKD patients and vascular calcification, but is not enough to explain the recent epidemiologic finding that higher serum phosphorus levels within the normal range (0.9–1.4 mM phosphorus) can be a risk factor for CVD in persons with normal kidney function.[12,13,71] Elevation of extracellular phosphorus causes endothelial dysfunction in vitro and in vivo. In addition, in vitro experiments demonstrated that high phosphorus loading inhibited nitric oxide (NO) production through increased reactive oxygen species (ROS) production and endothelial NO synthase (eNOS) inactivation via conventional protein kinase C (PKC), resulting in impaired endothelium-dependent vasodilation.[72] Dietary phosphorus loading can reduce flow-mediated vasodilation in healthy men, suggesting that dietary phosphorus loading or elevation of serum phosphorus level may be a risk factor for CVD in healthy persons as well as CKD patients. Thus, both endothelial dysfunction and medial calcification are closely associated with development of CVD (Figure 3). In accord with other large observational studies,[73,74] subjects with higher serum phosphorus concentrations have a more favorable profile of traditional CVD risk factors than those with lower serum phosphorus concentrations, suggesting that previously observed associations between serum phosphorus concentrations and incident CVD events are unlikely to be a result of differences in traditional CVD risk factors. Notably, subjects with higher serum phosphorus concentrations have a less favorable profile than some nontraditional CVD risk factors (i.e., higher serum C-reactive protein levels and lower serum 25(OH)D levels), which might partly contribute to increased peripheral arterial stiffness and to the relationship between serum phosphorus levels and risk for incident CVD events. Higher serum phosphorus concentrations, albeit within the normal range, have been associated with development of atherosclerosis, and carotid intima media thickness in the general population, as well as with mortality in patients with normal kidney function and in the Framingham Offspring study participants.

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These findings suggested that long-term excessive phosphorus loading, even if it does not cause hyperphosphatemia, can be a risk factor for CVD.

Cardiovascular disease in chronic kidney disease

CVD is the most important factor contributing to life expectancy in CKD.[68,75] Higher serum phosphorus levels are emerging as a novel biomarker of cardiovascular risk. In long-term dialysis patients, increased serum phosphorus concentrations have been consistently associated with arterial calcification and mortality independent of traditional atherosclerotic risk factors,[76–78] and with cardiovascular events and mortality in individuals with moderate CKD and those with normal kidney function.[11–13] Of 3,368 participants in the Framingham Offspring Study without clinically apparent kidney disease or CVD, each 1 mg/dL increase in serum phosphorus concentration was associated with a 31% increased risk of a first major cardiovascular event, and of 4,159 participants in the Cholesterol and Recurrent Events (CARE) Study, each 1 mg/dL increase in serum phosphorus concentration was associated with a 27% greater risk of all-cause mortality.[11,13] Experimental data showing that excess phosphorus promotes left ventricular hypertrophy, arterial calcification, and renal injury suggest a causal link between increased serum phosphorus and adverse outcomes.[79–81]

Phosphorus and hypertension

A few previous epidemiological studies have assessed the association of phosphorus intake with blood pressure levels. In the International Study of Macro- and Micro-Nutrients and Blood Pressure, which included 4,680 individuals from Japan, China, the United States, and the United Kingdom whose diets were assessed with multiple 24-h recalls, increments of 2 SDs in phosphorus intake were associated with 2.2 mmHg and 1.7 mmHg lower systolic and diastolic blood pressures, respectively, in multivariate analysis.[82] Similar results were found among 615 men of Japanese ancestry living in Hawaii, with those in the upper quintile of phosphorus intake, measured with one 24-h recall, having 3.2 mmHg lower systolic blood pressure and 2.0 mmHg lower diastolic blood pressure than those in the lowest quintile, after adjusting for age and body mass index.[83] Finally, a cross-sectional analysis of 4,519 US National Health and Nutrition Examination Survey 1999–2004 participants found that higher phosphorus intake, also assessed with one 24-h recall, was weakly associated with lower blood pressure (⁻0.04 and ⁻0.03 per each 100 mg of phosphorus per day),[84] although results in the opposite direction were found in US National Health and Nutrition Examination Survey I (1971–1975).[85] Phosphorus intake was associated with the risk of hypertension after adjustment for nondietary factors but not after additional adjustment for dietary variables. Phosphorus from dairy products, but not from other sources, was associated with lower baseline blood pressure and reduced risk of incident hypertension (Figure 4).[86] Thus, dairy foods, but not phosphorus, per se, might have a beneficial effect on blood pressure.

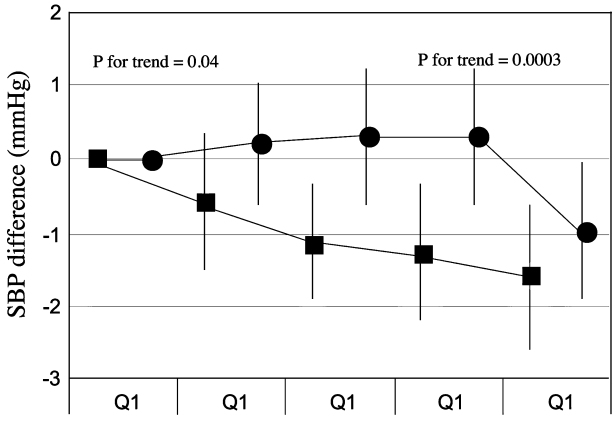

Figure 4 **Phosphorus intake and systolic blood pressure.** Cross-sectional difference in systolic blood pressure (SBP) levels (and 95% confidence intervals) by quintiles of phosphorus from dairy products (squares) and phosphorus from non-dairy foods (circles). Reproduced from Alonso et al. (2010)[86] with permission.

Dietary phosphorus loading has been associated with impaired endothelium-dependent vasodilation.[77] Also, higher phosphorus intake could lead to lower levels of circulating $1,25(OH)_2D$, with lower serum levels of vitamin D associated with higher blood pressure levels.[87] Elevated serum phosphorus levels could increase the risk of cardiovascular events.[12,13,88] Alternatively, it might be other nutrients in dairy foods, such as calcium, magnesium, potassium, and lactopeptides, or their combination, that are effective in reducing blood pressure levels and the risk of hypertension.[89] Concerning calcium, meta-analyses of randomized, controlled trials yielded an inverse association[90,91]; the recent estimated reduction in systolic/diastolic pressure was ⁻1.9/⁻1.0 mm Hg for calcium supplementation averaging 1,200 mg/day based on 23 trials (764 participants) of hypertensive and 27 trials (1,728 participants) of nonhypertensive individuals.[92] For magnesium, a meta-analysis of randomized clinical trials reported a reduction in systolic/diastolic blood pressure of ⁻0.6/⁻0.8 mmHg for magnesium supplementation averaging 375 mg/day, based on 14 trials (467 participants) of hypertensive and 6 trials (753 participants) of nonhypertensive individuals.[93] Dietary calcium and magnesium, correlated with phosphorus,

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were inversely associated with blood pressure.[82] Blood pressures were lower by 1.9–4.2 mmHg systolic/1.2–2.4 mmHg diastolic for people with intakes above versus below country-specific medians for all three of the minerals. These findings could indicate an effect of phosphorus in conjunction with other dairy constituents. Because changes in phosphorus intakes and other mineral compositions with these combination diets were part of multiple dietary modifications, their separate impact on blood pressure cannot be estimated from the above studies.

PHOSPHORUS INTAKE AND HEALTH

Role of phosphorus in health and disease

Greater serum phosphorus concentrations may reflect a relatively atherogenic diet. Phosphorus is abundant in beef, milk, butter, cheese, and processed foods, which also contain high levels of saturated fats and cholesterol. However, dietary intake patterns may not inform circulating phosphorus levels because key regulatory hormones, urinary excretion, and cellular flux serve to maintain serum phosphorus concentrations within a narrow range.[53,94] For dietary prevention of CVD, therefore, it is necessary to consider the contributions of both postprandial elevation of serum phosphorus and continuous elevation of serum phosphorus to the development of CVD. The former would be associated with endothelial dysfunction and progress of atherosclerosis, and the latter would be involved in medial calcification and progress of Mönkeberg-type arteriosclerosis. Until now, the effect of dietary phosphorus intake on vascular function has been underestimated, even though the association between serum phosphorus and vascular dysfunction has been thoroughly investigated, because fasting serum phosphorus levels did not increase in healthy persons, even if dietary phosphorus was overloaded.[69,95] However, postprandial phosphorus elevation was associated with %FMD in humans.

Excessive intake of certain nutrients, such as protein, phosphorus, and vitamin A, may have a negative impact on bone and mineral metabolism. Elevated protein and phosphorus intake is associated with higher renal loss of calcium, increased PTH secretion and higher bone resorption of calcium, phosphorus, and magnesium.[59,60] On the other hand, studies investigating the relationship between nutrient intakes and bone metabolism did not demonstrate that phosphorus per se induced bone loss.[96–98] It was reported that the wide use of phosphorus as a food additive in processed foods carries a risk of facilitating excessive phosphorus intake, which has a negative impact on calcium metabolism. In addition, an insufficient calcium-to-phosphorus ratio in the diet leads to osteoporosis and bone fractures.[99–101] Furthermore, phosphate is considered to be the major dietary source of acid.[64] Many foods in the modern diet are considered detrimental to bone health, under the acid-ash hypothesis, due partially to their phosphorus contents.

The highest rates of milk consumption decreased vascular events and ischemic heart disease by 16% in a pooled estimate of relative risk of heart disease from 10 prospective cohort studies.[102] Similarly, milk consumption lowered the risk of ischemic stroke, especially in those who had experienced a prior vascular event, in a 20-year prospective study of 2,403 men.[103] High-fat dairy products have been associated with increased risk of CVD in contrast to skim milk.[104] Similarly, low-fat more than high-fat dairy products were found to be inversely associated with risk of hypertension in women.[105] Dairy consumption has been positively linked to bone health in observational, retrospective, and intervention studies. Two reviews of the literature found that 25 of 32 observational studies and 11 of 11 randomized controlled trials showed a significantly positive association between dairy food intake and bone mineral density or bone mineral content.[106,107] The benefits of dairy consumption for bone health are strongest during growth periods. Milk constituents thought to influence bone health include calcium, protein, potassium, phosphorus, magnesium, zinc, vitamin B_{12}, and vitamin D when fortified. Calcium, phosphorus, magnesium, and zinc play a structural role in the formation of hydroxyapatite crystals that comprise bone mineral content. Calcium also reduces bone remodeling rates through PTH suppression.[108] Phosphorus intake causes considerable alterations in the PTH physiology. A diet containing low calcium or high phosphorus and/or a diet with a calcium-to-phosphorus imbalance induces the hormone secretion that leads to secondary hyperparathyroidism.[109–111] Certain effects of this dietary-induced hyperparathyroidism on bone health have been demonstrated in animal and human studies.[112–114] Therefore, the dietary calcium-to-phosphorus ratio is considered a marker for the prediction of bone health and/or quality, independent of the absolute intake of both elements separately.[115,116] Adequate nutrition plays an important role in bone mass accrual and maintenance and has been demonstrated to be a significant tool for the prevention of fractures in individuals with osteoporosis. Not only calcium, but also protein, phosphorus, magnesium, and vitamin D and K intakes are important factors related to bone health.[110,117] A number of prospective cohort studies have found a reduced risk of hypertension in individuals with higher dairy product intake (particularly low-fat dairy),[118–123] including a recent analysis from the ARIC cohort.[124] Parallel to these results, calcium from dairy products, but not from other sources, was associated with lower risk of hypertension in another prospective

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study.[120] The results highlight the importance of focusing on foods, in addition to nutrients, in nutritional epidemiology[125] and offer additional evidence of the potential beneficial effect of dairy foods on blood pressure.

Dairy foods contribute 70.3% of calcium, 16% of magnesium, almost all of the vitamin D, 18.2% of vitamin B_{12}, 15% of zinc, and 25% of riboflavin in the US diet.[106] Milk consumption has been called a marker for an overall healthy diet because of its association with increased nutrient intake.[126–128] Several studies have demonstrated the difficulty in meeting dietary requirements for calcium, potassium, and several other nutrients when milk is largely excluded from the diet. An analysis of data on adolescents in the NHANES 2001–2002 survey showed that those who excluded dairy could not meet calcium recommendations within the current dietary consumption patterns because of not choosing alternative calcium-fortified foods.[129] As an example, for the 2005 *Dietary Guidelines for Americans Advisory Committee Report*, it was determined that without milk products, 19–50-year-old women would reach only 44% of the calcium recommendations, 57% of the magnesium recommendations, and 57% of the potassium recommendations, as an example.[106]

Phosphorus intake and chronic kidney disease

A dietary approach to phosphate retention in advanced renal failure patients and a dietary approach to phosphorus reduction are important steps in the treatment of hyperphosphatemia. The level of expression of klotho mRNA was greatly reduced in the kidneys of all chronic renal failure patients. Dietary phosphorus restriction induced klotho expression, which enhances the beneficial effect of phosphorus restriction in patients with chronic renal failure and or on hemodialysis. However, dietary restriction cannot considerably reduce the level of phosphorus retention. Although some of the foods that contain a moderate level of phosphorus cannot be too tightly restricted due to their protein content, foods with a high phosphorus-to-protein ratio may be limited. These are foods such as cheese, eggs, organ meats, and seafood. Despite equivalent protein and phosphorus concentrations in the diets, subjects had lower serum phosphorus levels, a trend toward decreased urine 24-h phosphorus excretion, and significantly decreased FGF23 levels when fed a vegetarian diet compared with a meat-based diet.[34] These results, if confirmed in longer-term studies, provide a rationale for recommending a predominance of grain-based vegetarian sources of protein to patients with CKD. This will allow increased protein intake without adversely affecting phosphorus levels. Other foods that are high in phosphorus are processed foods, such as processed meats, which contain phosphorus-based additives to improve the consistency and appearance of the food. As people are becoming more reliant on processed and packaged meals due to convenience, phosphorus from these sources needs to be considered by clinicians and dietitians when advising patients on diet. However, the ingredients that contain phosphorous are difficult for consumers to check as they tend not to be listed as an ingredient on food packaging; therefore, patients may inadvertently consume foods that are high in phosphorus. Some food items, such as processed chicken products, which are high in protein, have almost double the amount of phosphorus as fresh chicken. Fresh meat is considered suitable for someone following a phosphorus restriction diet; however, processed foods may, in fact, be providing much more phosphorus than realized.[22] In order to help improve patient care with regards to hyperphosphatemia, diet should be reviewed and the impact of processed foods should be considered in addition to the common foods with a high phosphate-to-protein ratio. In order for patients to be more aware of the phosphate contents of food, it would be beneficial for phosphorus content to be indicated on food labels or for the data to be available for health professionals to access.

CONCLUSION

Estimation of the dietary intake of phosphorus should take into consideration both the phosphorus contained in natural foods and the phosphorus added to processed foods. An investigation of products that reported the use of additives on their labels had an average phosphate-to-protein ratio that was 28% higher than additive-free products.[19] The impact of the addition of phosphorus to processed food is likely to be clinically significant, especially in view of the probability that phosphorus in food additives is much more readily absorbed than phosphorus contained in unprocessed foods.[22,130] The lack of attention by practicing nephrologists to dietary phosphorus restriction in general and, more specifically, the lack of awareness regarding the increasing consumption of processed foods that are rich in phosphate additives, may significantly limit the efficacy of current interventions.[131] Moreover, in many countries food labels and other sources of reference do not include the product's phosphate content, and variations in phosphate content among similar products prevent patients and dietitians from accurately estimating food phosphorus content and, therefore, phosphorus intake. As a result, there can be large gaps between estimated and actual phosphorus intake levels. This implies that better reporting of the phosphorus content of foods by manufacturers could result in improved control of dietary phosphorus and that voluntarily adding the phosphate content to the nutritional composition label should be considered. This will

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enable not only patients but also healthy persons to make informed choices about the food they eat with regards to phosphate.

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