Phosphorus[1]

A ubiquitous mineral in nature and the second most abundant mineral in the human body, phosphorus represents ~1% of total body weight. With both an extracellular and intracellular distribution, phosphorus functions as a structural component of bones and teeth and DNA/RNA and enables the bipolarity of lipid membranes and circulating lipoproteins. Metabolically, phosphorus functions in critical pathways to produce and store energy in phosphate bonds (ATP), buffer blood, regulate gene transcription, activate enzyme catalysis, and enable signal transduction of regulatory pathways affecting a variety of organ functions ranging from renal excretion to immune response (1). Less than 1% of unbound inorganic phosphate (PO_4^-) in the extracellular space is metabolically active and is now considered tightly maintained within a narrow serum concentration range (2.5–4.5 mg/dL) in adults. Maintenance of phosphorus homeostasis in adults involves keeping urinary losses equivalent to net phosphorus absorption and equal amounts deposited and resorbed from bone. Until recently, the kidney has traditionally been held as the main organ functioning in the maintenance of phosphorus homeostasis relying on parathyroid hormone (PTH)[2] and vitamin D regulation. However, it is now evident that a more complex organ network system (bone-kidney-intestine) is involved in the homeostatic control of serum phosphate within the normal range. This bone-kidney-intestine network operates through complex, ordered multiple endocrine negative feedback loops between PTH, fibroblast growth factor 23 (FGF-23), Klotho, and vitamin D (2).

Deficiencies

In the absence of genetic disorders, tumor-related phosphate wasting, or aberrant dietary problems such as re-bound feeding in anorexia or alcoholism, phosphorus deficiency or hypophosphatemia is rare in the healthy population, which is probably due to the widespread availability of phosphorus in most foods.

Dietary Recommendations

Serum inorganic phosphate was proposed as a biomarker to assess phosphorus nutritional adequacy by the Institute of Medicine to establish the dietary intake guidelines for phosphorus in 1997, which are shown in **Table 1** (3). The Tolerable Upper Intake Level (UL) of phosphorus remains controversial because the data used to arrive at this upper level of safe intake were based on an equation derived from phosphorus infusion studies and were not based on dietary phosphorus intakes. In addition, in 1997 there was limited understanding of the now-known compensatory endocrine pathways and circadian fluctuations inherent to serum phosphate that may have influenced this decision (4–6). In contrast to the use of serum phosphate data by the Institute of Medicine to establish DRIs for the United States and Canada, the European Food Safety Authority does not consider serum phosphate to be a reliable biomarker for phosphorus nutritional adequacy and elected to use other criteria for setting Dietary Reference Values for phosphorus (4). Phosphorus intakes for various age and gender groups from the 2011–2012 nationally representative US nutrition survey are shown in Table 1 along with the 1997 DRIs for phosphorus intake. **Table 2** shows phosphorus intakes over age and gender collected in a nationally representative Finnish nutrition survey (2011–2012) (7) and the Nordic Dietary Reference Value for phosphorus (8). The most recent national nutrition surveys reveal that total phosphorus intake exceeds the intake guidelines in the United States and in Finland for most ages and genders, with the exception of teens and young women, who have the highest phosphorus requirements, presumably due to the increased need during rapid bone growth.

Food Sources

Phosphorus is widely distributed in the global food supply, with milk and dairy being the greatest contributors followed by meat and poultry. The total content of phosphorus in foods, as well as the chemical nature and physiologic characteristics of absorption,

TABLE 1 1997 DRI guidelines for phosphorus and daily intakes for men and women in the NHANES 2011–2012 survey[1]

Age, y	UL, mg/d	RDA, mg/d	EAR, mg/d	Daily intake, mg/d	
				Men	Women
6–11	3000	500–1250	380–1055	1347 ± 26 (590)	1225 ± 26 (556)
12–19	4000	1250	1055	1700 ± 56 (585)	1162 ± 32 (567)
20–29	4000	700	580	1692 ± 43 (457)	1226 ± 20 (428)
30–39	4000	700	580	1822 ± 69 (425)	1330 ± 40 (404)
40–49	4000	700	580	1805 ± 61 (374)	1193 ± 40 (407)
50–59	4000	700	580	1544 ± 82 (382)	1183 ± 36 (423)
60–69	4000	700	580	1561 ± 39 (397)	1137 ± 41 (380)
≥70	3000	700	180	1350 ± 36 (359)	1060 ± 26 (365)

[1]Values are means ± SEs (*n*) unless otherwise indicated. Values for phosphorus intake are estimated directly from day 1 dietary intake data and do not reflect the usual mean intake estimates approach used to estimate the distribution statistics. Data are from What We Eat in America, NHANES 2011–2012, nutrient intakes from food (data available from www.ars.usda.gov/nea/bhnrc/fsrg). EAR, Estimated Average Requirement; UL, Tolerable Upper Intake Level.

[2]Abbreviations used: FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; UL, upper level of safe intake.

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TABLE 2 Finnish National Survey phosphorus intakes and DRVs for phosphorus[1]

Age, y	UL, mg/d	RI, mg/d	AR, mg/d	Daily intake, mg/d	
				Men	Women
25–34	3000	600	450	1891 ± 661	1474 ± 411
35–44	3000	600	450	1758 ± 600	1483 ± 541
45–54	3000	600	450	1761 ± 650	1305 ± 371
55–64	3000	600	450	1606 ± 539	1356 ± 445
65–74	3000	600	450	1574 ± 569	1252 ± 382

[1]Values are means ± SDs unless otherwise indicated. Values for phosphorus intake are based on 48-h recall data (7). AR, average requirement (corresponds to the Estimated Average Requirement); DRV, Dietary Reference Value; RI, recommended intake (corresponds to the RDA); UL, Tolerable Upper Intake Level.

will influence the hormonal regulation of phosphorus balance. There are 2 basic types of phosphorus in the food supply, natural and added, often referred to as organic and inorganic, which have very different rates and efficiencies of absorption. Natural or organic phosphorus is slowly and less efficiently (40–60%) absorbed, whereas inorganic phosphorus salts added to food in processing are rapidly and efficiently (80–100%) absorbed (5). Accurate estimates of the total phosphorus content of processed, convenience, and fast foods, specifically the contributions from physiologically active food additives, require information about the quantity and characteristics of added phosphorus in these foods. This information is currently not captured by the various dietary instruments used to assess dietary intakes (5).

Clinical Uses

The clinical uses of phosphorus supplements are limited to situations described above, such as inherited disorders of phosphorus metabolism or other medical causes of hypophosphatemia or phosphorus wasting.

Toxicity

The inability to accurately access total phosphorus intake hinders our understanding of phosphorus toxicity and has called into question the applicability and accuracy of the 1997 UL, as shown in Table 1 (3–5). The European Union expert panel decided against establishing an upper limit of safe phosphorus intake due to the lack of clear evidence on which to base it (4). The Nordic Nutrition Recommendations (8) stated that a provisional UL of 3000 mg/d is to be used based on the European Food Safety Authority evaluation that healthy persons can tolerate intakes of ≤3000 mg/d. Nonetheless, dietary phosphorus intake is on the increase in Western cultures due to the growing availability and preference for processed foods, a consideration that has stimulated worry that phosphorus food additives could increase serum phosphate in the general population. Increased mortality and cardiovascular disease risk with high serum phosphate concentrations were initially shown in patients with chronic kidney disease; and recently, phosphorus intakes in excess of the nutrient needs of the healthy population appear to be contributing to disordered mineral metabolism, vascular calcification, impaired kidney function, and bone loss (6). As yet, few studies have linked high dietary phosphorus intake to mild changes in serum phosphorus and disordered endocrine regulation. This is likely due to difficulties in accurately assessing the nature and total amount of phosphorus ingested (5). Although phosphorus is an essential nutrient, its excess could be linked to tissue damage by a variety of mechanisms involved in the endocrine regulation of extracellular phosphorus as shown in patients with chronic kidney disease (2). Disordered regulation of these hormones by high dietary phosphorus intake may be key factors contributing to renal failure, cardiovascular disease, cancer, and osteoporosis in healthy adults, which are important questions in ongoing research (9–12).

Recent Research

We describe some recent research activities exploring the mechanisms and possible links between high phosphorus intake, particularly from phosphorus food additives, and specific chronic disease risk in free-living individuals with healthy renal function. Animal studies show that high inorganic phosphate feeding resulting in high serum phosphate promoted lung, skin, and bladder cancer. Prospective epidemiology studies in healthy populations and in vitro studies exploring potential pathways and mechanisms through which high extracellular phosphate from excess phosphorus intakes may initiate or increase the incidence of cancer are underway (9). Clinical investigators are examining the effects of natural compared with added phosphorus in foods commonly consumed by free-living individuals, their effect on PTH levels, and their potentially harmful effects on bone, which may contribute to osteoporosis, particularly in women (10). Special dietary assessment tools are being developed to determine the relative contribution of phosphorus-containing food additives to habitual dietary intakes. This information is used in cross-sectional studies to assess the relation between food additive intake and specific cardiovascular disease risks represented by the measurement of a validated risk factor such as carotid intima-media thickness (11). Several nationally representative nutritional surveys with appropriate follow-up periods for the clinical endpoints studied are examining the relation between total phosphorus intake and all-cause mortality, incident prostate cancer, and other diseases. Because of their large size, these studies are limited by their inability to differentiate natural from added sources of phosphorus in the foods consumed (12).

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