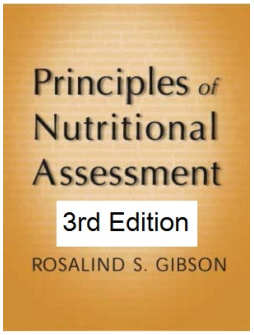

Calvo MS[1], Whiting SJ[2], and Uribarri J[1], Principles of Nutritional Assessment: phosphorus

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Abstract

The essential nutrient phosphorus (in nature occurring as phosphate) is ubiquitous in all the foods we eat, the human body and, in effect, all living organisms. phosphate is critical to structural and biochemical functions needed to secure energy, reproduce and grow. Most of the body's phosphate is contained within bones, teeth, membranes and intracellular spaces; however, it is the 1% present in the extracellular space, serum that is clinically measured to inform about physiologic and nutritional phosphate status.

Serum phosphate in healthy individuals usually reflects phosphate balance that is maintained within a narrow range by hormonal control of renal reabsorption and excretion and intestinal absorption when dietary phosphate intakes are low or excessive. Regulation of serum phosphate involves the interplay of four organs (kidneys, intestine, bone and parathyroid glands), phosphate transporters membrane bound in these organs, and the actions of three endocrine hormones (parathyroid hormone, calcitriol the active form of vitamin D, and bone-secreted fibroblast growth factor-23 (FGF-23), all of which influence the activity of the phosphate transporters to increase or decrease absorption, reabsorption or excretion of phosphate.

Hyperphosphatemia, serum phosphate > 1.45mmol/L, is often related to excess dietary phosphate intake with consumption of phosphate additive-rich processed foods or the typical Western diets when kidney function is impaired. Higher serum phosphate has been associated with disruption of endocrine pathways that may link high phosphate intake with pathology associated with chronic disease risk including cardiovascular disease. In contrast, hypophosphatemia, < 0.87mmol/L, is rarely related to dietary deficiency of phosphate except in cases of severe malnutrition and more likely due to inborn errors of metabolism or tumor production of excess FGF-23 that causes renal phosphate wasting and bone disease (rickets and osteomalacia).

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23b.1 phosphorus

phosphorus is the 11th most abundant element yet phosphorus is not present in nature as elemental phosphorus, instead occurring mainly bound to oxygen as phosphate (Ferro, 2018). Deposits of phosphate-rich rock in the earth's crust slowly release phosphate which builds up in soils over time, entering the food chain via soil microbes, and then crops, livestock, and other components of the human food supply. However, deposits of rocks rich in phosphate are limited across the globe. When mined, these phosphate deposits are largely used as fertilizers for crop growth (Ferro, 2018).

Phosphorus is often the key growth-limiting factor for all living things. As an essential nutrient, phosphorus functions in critical pathways and cellular components in all life forms on earth, ranging from subcellular viruses to complex plants and animals, all dependent on phosphate for energy, growth, reproduction, structure, and homeostasis facilitated through signal transduction. phosphates participate in all biological processes providing energy stored in phosphodiester bonds of ATP (the phosphodiester backbone of RNA and DNA). Other functional roles include the structural integrity of cell membranes as phospholipids, regulation of acid base balance, mineralization of teeth and bones, lipid transport in blood, and signalling pathways essential to maintaining phosphate homeostasis. As phosphate has such a critical role in so many biological processes, phosphate homeostasis must be tightly regulated. In conditions when sources of phosphate are deficient, growth or reproduction is limited, whereas with excess, toxicity may occur, which in humans may manifest as disease (Hernando, 2021).

23b.2 Biological Forms of phosphate and their measurement

The three forms of phosphorus bound to oxygen that occur in nature are shown in figure23b.1: an ionic anion, an inorganic salt, and as an organic compound, using phytate as the example. Inorganic or mineral phosphate largely comprises the different salts of orthophosphate that occur in greater abundance than pyrophosphate. Within the pH range of the human body, the two main forms of orthophosphates are $H_2PO_4^{-1}$ and HPO_4^{2}. The organic form of phosphate occur when bound to a carbon atom of protein, lipids, nucleic acids, and other organic compounds, usually through phosphate ester linkages. The total body phosphate content in an adult human is about 900g of elemental phosphorus, existing mainly in the skeleton and teeth, with less amounts in soft tissues.

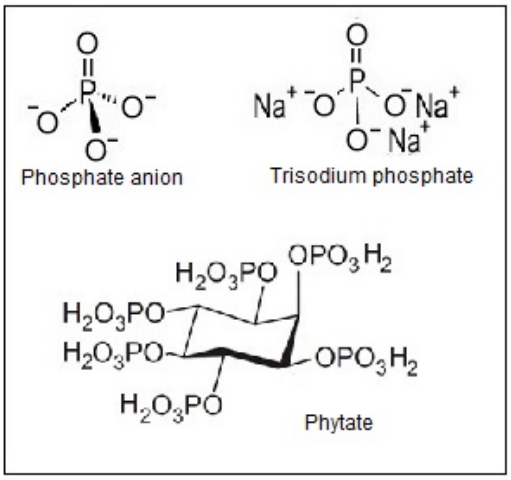

figure23b.1 phosphate anion, Trisodium phosphate, and Phytate — the latter redrawn from Marolt and Kolar (2021)

The phosphate in bone and teeth is present as calcium phosphate hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). Less than 1% of phosphorus occurs in the extracellular space. Intracellular phosphate consists largely of organic molecules such as creatine phosphate, ATP, nucleic acids, phospholipids and phosphoproteins in concentrations of phosphate of about 1mmol/L.

Clinically, the terms phosphate and phosphorus are used interchangeably. However, because elemental phosphorus does not occur in the human body, phosphorus is usually measured asmg phosphate and can be converted to molar P concentration by dividing the measured weight inmg by the atomic weight of P (31). Table 23b.1.

Sample	Reference Ranges	
	mg/dL	mmol/L
Cord	3.7 – 8.1	1.2 – 2.8
Child	4.5 – 5.5	1.45 – 1.78
Adult	2.7 – 4.5	0.87 – 1.45
Older Adult > 60y	M: 2.3 – 3.7 F: 2.8 – 4.1	M: 0.74 – 1.2 F: 0.90 – 1.3

Table 23b.1 Normal Inorganic Serum phosphate Values for Children and Adults. For more information on disorders of serum phosphate see (Koumakis et al., 2021).

23b.3 Interpretive Criterion: Serum phosphate

Serum phosphate is the most frequently used biomarker of phosphorus status in a clinical setting, and is usually measured in the fasting state. However, the measurement of a single fasting serum phosphate concentration represents only a small portion of the total body phosphate, and hence does not always reflect the body phosphate stores. Measurement of serum or plasma phosphate concentration requires the use of anticoagulants such as heparin which do not interfere with the color reaction described for the AOAC spectrophotometric method described in 23b.2. Hemolyzed samples are not suitable for phosphate measurement as erythrocyte phosphate confounds the measurement and hemoglobin contributes color interference. Serum phosphate concentrations can also be affected temporarily by acute shifts of phosphate between intracellular and extracellular compartments without affecting total body content (Uribarri & Oh, 2018).

Serum phosphate concentrations are maintained within a narrow range (see Section 23b.5 for details of the hormonal regulation of serum phosphate). In adults, total serum inorganic phosphate ranges between 0.87-1.45mmol/L (56% is ionized, 20% bound to protein and 24% bound to other cations); however, there is a significant amount of organic phosphate in serum (7.5–8.0mg/dL or 2.4–2.6mmol/L) which is not included in the analytical method used by clinical laboratories. When serum phosphate concentrations fall below the normal range, a condition called hypophosphatemia occurs, whereas for concentrations above the normal range, hyperphosphatemia develops; serious clinical consequences can arise from both conditions.

Several factors affect serum phosphate concentrations. Diurnal variation in serum phosphate occurs with concentrations lowest at 9AM and highest at 7PM. There is also a seasonal variation, whereby levels are higher during the summer than during the winter; this may arise because phosphorus absorption is stimulated by the greater synthesis of vitamin-D with higher summer sunlight exposure. Serum phosphate is also higher in women than in men (by about 0.31mg/dL, 0.1mmol/L), and higher in children (i.e., normal range 1.45–1.78mmol/L) than adults (i.e., normal range 0.87–1.45mmol/L); see Table 23b.1.

Normal serum phosphate values for children and adults are shown in Table 23b.1. Hypophosphatemia is usually defined as serum phosphate < 0.87mmol/L and hyperphosphatemia as a serum phosphate > 1.45mmol/L; see Section 23b.8 for more discussion of abnormalities in serum phosphate (Koumakis et al., 20210).

23b.4 phosphate Balance

Phosphate balance is the result of the interaction of intestinal absorption of dietary phosphate, renal phosphate excretion, and exchange of phosphate between extracellular and bone and intracellular phosphate pools (Figure 23b-2.). At present, the only easily available parameter to study total body phosphate in a clinical setting is to measure the serum phosphate concentration, usually in the fasting state. This measurement represents only a small portion of the total body phosphate, as noted above, and can also be affected by shifts of phosphate between intracellular and extracellular compart ments (Uribarri & Oh, 2018). (Figure 23b.2).

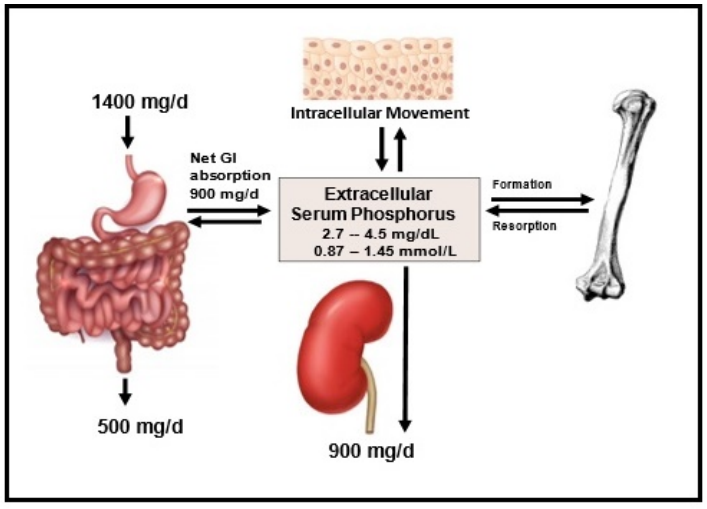

Figure 23b.2 The diagram illustrates phosphorus balance maintained in a healthy adult consuming an average American diet containing 1400mg phosphate (Pi). The components of phosphorus or phosphate balance, include intestinal absorption, kidney excretion, bone formation/resorption, the intracellular space, and plasma transport. Under conditions of normal renal function, the amount of Pi absorbed equals the amount excreted in the urine, thus balance is achieved in an adult where bone formation equals bone resorption and tissue uptake equals that released.

The kidneys play a major role in phosphate balance by adjusting urinary excretion (output) to match net gastrointestinal absorption (input) of phosphate to maintain zero balance in an adult or, to retain phosphate to maintain positive balance in a child for growth, or for a pregnancy. In healthy subjects, the kidneys reabsorb about 89% of the filtered load of phosphate, with the rest being excreted in the urine. Plasma phosphate filtered in the glomerulus is mainly reabsorbed in the proximal renal tubules (75%), with only 10% reabsorbed in the distal tubules, leaving about 10–15% in the urine.

Gastrointestinal (GI) phosphate absorption in humans has traditionally been measured as the difference between dietary and fecal phosphate content; this net phosphate absorption is a linear function of dietary phosphate intake (IOM, 1997). For a dietary phosphate intake within the range of 4–30mg/kg/day (280–2100mg per day for an adult), net absorption is about 60–65%. Shown in Figure 23b.3, there are two main transport systems for intestinal phosphate

absorption: one is an active, sodium-dependent, saturable and transcellular transporter, and the other is a passive, sodium-independent, non-saturable and paracellular transporter (Marks, 2019). The intestinal sodium-dependent transporter is regulated by vitamin D and parathyroid hormone (PTH) and is often referred to as “active” transport. In contrast, the paracellular phosphorus absorption pathway lacks a tight regulation and depends on the phosphate concentration gradient across the epithelium, the electrical gradient (lumen negative), and tight junction permeability (Calvo & Uribarri, 2021).

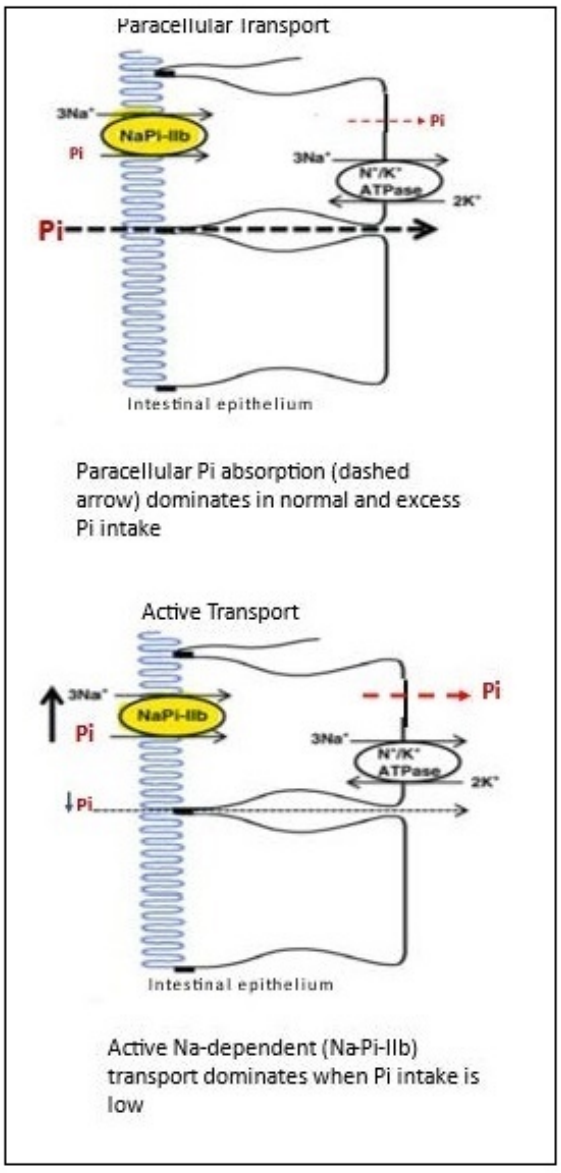

Figure 23b.3 Mechanisms of Intestinal phosphate Absorption (Modified from Marks, 2019)

figure23b.3 Most organic and inorganic phosphate is absorbed in the small intestine after liberation by gut and intestinal enzymes. However, the dominant plant source of phosphate, phytate (Figure 23b-1), is poorly absorbed in humans because of lack of the enzyme phytase. Many colonic bacteria produce phytases (myo-inositol hexakisphosphate phosphohydrolases) capable of sequentially hydrolyzing phytate, releasing phosphate. Liberated inorganic phosphate then has the potential to be absorbed in the colon via paracellular transport, although the overall importance of this remains uncertain. Increasing solidity of distal colon fecal contents could potentially make soluble phosphate less accessible for paracellular absorption. Nevertheless, a recent review concluded that at least 50% of phosphate present in phytate is recovered as phosphate in 24-hour urine collections based on results of a series of earlier human studies (Calvo & Uribarri, 2021).

23b.5. Hormonal Regulation of Serum phosphate

Serum phosphate concentration must be maintained within a very narrow range to avoid adverse health consequences and risk of disease such as soft tissue calcification or cardiovascular disease. Regulation of serum phosphate involves the interplay of four organs, phosphate transporters membrane bound in these organs, and the actions of three endocrine hormones that influence the activity of the phosphate transporters (Uribarri & Calvo, 2023). The four major organs involved in regulating serum phosphate are the kidneys, bone, intestine, and parathyroid glands. There are two families of sodium-phosphate membrane transporters specific to these organs. They include the SLC34 group of NaPi-2a, b, c, chiefly located in the kidney and intestine, and the SLC20 family (PiT-1 and 2) largely found in bone, intestine, soft tissue, muscle, with some in the kidney (Forester et al. 2013). The activity of these two families of sodium-phosphate membrane transVporters is controlled by three endocrine hormones: parathyroid hormone (PTH), calcitriol (1--25,dihydroxycholecalciferol; (1-25$(OH)_2$ D), the active metabolite of vitamin D), and fibroblast growth factor 23 (FGF-23). The three phosphate regulating hormones are

endocrine hormones meaning that they are secreted into the circulation by a specific organ, but act upon a distal organ.

As illustrated in Figure 23b.4, PTH is secreted by the parathyroid glands when the rise in serum phosphate triggers a decrease in serum ionized calcium or is sufficiently elevated to directly stimulate PTH secretion. Circulating PTH rapidly acts to decrease NaPi-2a and NaPi-2c co-transporters in the renal proximal and distal tubules. A decrease in membrane co-transporters acutely decreases phosphate reabsorption and increases phosphate excretion in the urine. When normal, serum phosphate concentration is filtered in the glomerulus, about 75% of phosphate is reabsorbed in the proximal tubule and 10% from the distal tubule with 10–15% lost in urine, as noted earlier. The action of PTH rapidly lowers serum phosphate by increasing urinary loss, and rapidly increases serum calcium and to a lesser degree phosphate by stimulating bone resorption PTH action more slowly restores serum calcium through up-regulation of the renal cytochrome enzyme Cyp27b1 that catalyzes the activation of 25-hydroxy vitamin D to the active metabolite, calcitriol ($1,25(OH)_2D$) secreted by the kidney into the circulation. In turn, the circulating hormonal form of vitamin D, calcitriol, acts on the small intestine to increase active calcium transport, thus PTH rapidly corrects serum phosphate and calcium concentrations that stray from the normal range (Uribarri & Calvo, 2023).

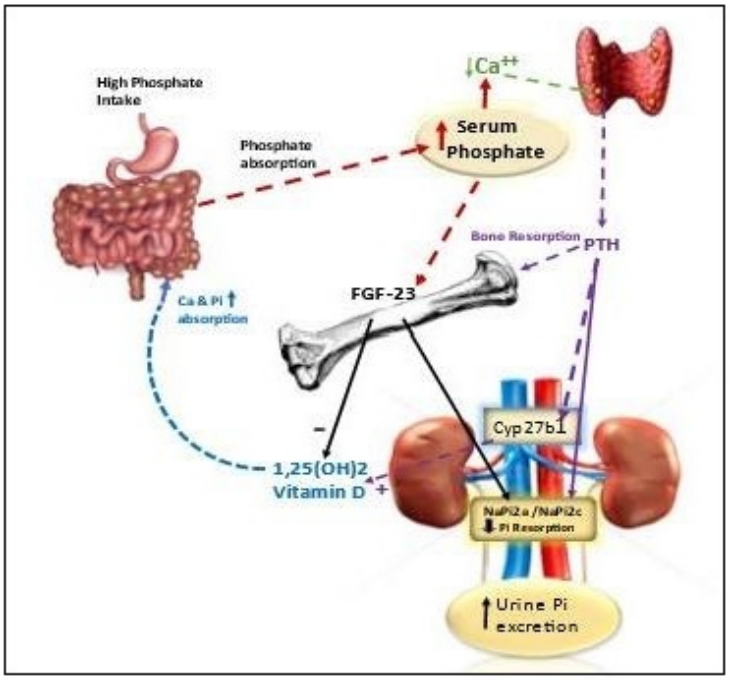

Figure 23b.4 Stimulatory pathways in the diagram are shown by dashed lines and inhibitory pathways by solid lines in red for hyperphosphatemia, purple for PTH, black for FGF-23 and blue for 1,25-dihydroxy vitamin D (calcitriol).

When excessive intake of phosphate is sustained over time, or kidney function fails resulting in hyperphosphatemia, hormonal control of serum phosphate is reliant on regulating intestinal phosphate absorption and renal tubular phosphate reabsorption and may require the action of the bone secreted hormone FGF-23 (Rausch & Foeller, 2022). In response to hyperphosphatemia, FGF-23 is secreted by osteocytes in bone and similar to PTH, FGF-23 acts to suppress co-transporter action (proximal tubule NaPi-2a and NaPi-2c), decreasing renal reabsorption and increasing urinary phosphate excretion but acts to supress PTH secretion (not shown) . In contrast to the action of PTH, FGF-23 inhibits 1,25-dihydroxy vitamin D renal synthesis and intestinal phosphate absorption by downregulating renal cytochrome P450 (Cyp27b1) expression (the key enzyme for calcitriol production), and enhancing renal Cyp24a1 production, thus catalyzing the inactivation of 1,25-dihydroxy vitamin D.

FGF-23 action may be dependent or independent of Klotho, a beta-glucuronidase enzyme that occurs as both a transmembrane protein and a secreted renal protein, and which can function as a co-receptor to FGF-23 (not shown in Figure 23b.4). Although many of Klotho's functions remain unclear, it has a proven role in phosphate regulation (Kuro-O, 2019). FGF-23 clearly suppresses calcitriol synthesis and, with time, PTH secretion; however, initially in response to high serum phosphate,

PTH is believed to stimulate FGF-23 secretion from osteocytes (Rausch & Foeller, 2022). Not shown in the simplified diagram of hormonal control of serum phosphate (Figure 23b.4), calcitriol upregulates Na-Pi co-transporters (an action opposite to that of FGF-23) in both the intestine and proximal renal tubules which leads to both increased intestinal absorption of phosphate and increased renal phosphate reabsorption. Calcitriol suppresses PTH secretion and has a negative feedback action on renal 1-alpha hydroxylase (Cyp27b1), thereby reducing its own production. With lower calcitriol concentrations, 24-hydrolxylase is upregulated, increasing the production of 24,25-dihydroxy vitamin D effectively inactivating calcitriol hormonal action.

23b.6 Nutrient Reference Values

In 1997, the Institute of Medicine (U.S. and Canada) determined adult age specific Estimated Average Requirement (EAR) values for phosphorus derived from studies using serum phosphorus as a biomarker (IOM, 1997). For adults 19–50 years, the EAR was based on the relationship between serum phosphate and absorbed intake determined from earlier published data. This relationship was then used to translate absorbed intake to the amount of ingested phosphorus based on an assumed efficiency of absorption of 62.5% from a mixed diet not high in phytate (Calvo & Whiting, 2018). An intake of phosphorus of 580mg/d meets the needs of 50% of the adult population (≥ 19y) and therefore was set as the EAR and served as the basis for determining the Recommended Daily Allowance (RDA) for phosphate that covers the phosphorus needs of 97% of the adult population. For children, the biomarker used to set the EAR for dietary phosphorus intake was based on published factorial estimates of accretion of phosphate into bone; see IOM (1997) for more details. For infants, the AI was set to reflect the observed mean intakes of infants fed principally with human milk (IOM, 1997).

The EAR and RDA values for phosphorus for infants, children and adults by age and sex, and for the physiologic states of pregnancy and lactation recommended in 1997, are shown in Table 23b.2. A tolerable upper intake level (UL) for phosphate was also set in 1997 as part of the Dietary Reference Intakes (DRIs). The UL is considered to be a safe intake level, but as intake increases above the UL, risk for adverse events increases (IOM, 1997). The UL for adults is set at 4000mg/d. Researchers now question the method used by the IOM panel that set a value nearly six times higher than the RDA for phosphorus is in question, suggesting a need to revisit the UL (Whiting & Calvo, 2018). The increased use of phosphate-containing food additives in processing led the European Food Safety Authority (EFSA) to reassess the safety of phosphate additives and cumulative phosphate intakes. The 2019 EFSA review resulted in a revision of the "group acceptable daily intake" (ADI) of 4.2g phosphate per day to the lower value of 2.8g phosphate per day for an average 70kg adult (EFSA, 2019).

Age/sex groups	EAR	RDA	UL
0–6 mo	--	100 (AI)	-
6–12 mo	--	275 (AI)	-
1–3y F & M	380	460	3000
4–8y F & M	405	500	3000
9–18y F & M	1055	1250	4000
19–50y F* & M	580	700	4000
51–70y F & M	580	700	4000
71+ F & M	580	700	3000

Table 23b.2 US and Canadian phosphorus Dietary Reference Intakes (mg P/day). Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA, or Adequate Intake equivalent) and Upper Level (UL) for phosphorus * Applies to pregnant and lactating women. Source: (Institute of Medicine, 1997).

Current mean dietary phosphate intakes of Americans are 2–3-fold higher than the RDA for all age groups > 1y (with

the single exception of rapidly growing adolescents), but do not exceed the current UL. Nonetheless, excess phosphate intake is associated with growing evidence of potential noncommunicable disease risk. This is of concern especially when considering the high intakes of bioavailable phosphate that may occur from the consumption of ultra-processed foods. Consequently, consideration should be given to revising the 1997 DRI's (notably the UL) (Uribarri &Calvo, 2022).

23b.7 Dietary Sources

Dietary sources of phosphate include both organic and inorganic phosphate. Phosphate is present in most food sources and is usually highest in animal protein compared to plant protein sources. Importantly, the bioavailability of phosphorus differs between protein derived from animal sources compared to plant derived protein. In addition to containing protein, plants store phosphate as phytate (Figure 23b.1). Phosphate is stored as phytate in unrefined cereals, oil seeds, and legumes that requires enzymatic or physical action to release phosphate bound to phytate. Bioavailability of phytate-phosphorus is low unless foods are processed using home-based methods such as soaking, germination, or fermentation, or commercial methods such as canning and extrusion (Tefarra, 2021), all of which having the potential to improve phosphate availability from phytate. While these methods of processing improve phosphate availability from phytate, commercial processing leading to processed and ultra-processed foods may involve the addition of phosphate-containing additives that provide highly available sources of phosphate, such as sodium phosphate salts shown in Figure 23b-1 (Calvo & Uribarri, 2021).

Examples of animal, plant, and additive sources of phosphate are shown in Table 23b.3, with the foods classified according to the NOVA system (Monteiro et al., 2017), which reflects their degree of processing. The NOVA system classifies foods into four groups, with the fourth group called "ultra-processed". A recent cross-sectional study of the United States food supply found that 71% of packaged foods and beverages were ultra-processed and 60% of energy intake came from ultra-processed foods, an increase over past decades (Baldridge et al. 2019).

High ultra-processed food consumption patterns are associated with increased risk of cardiovascular disease and mortality (Juul et al. 2021), chronic kidney disease (Cai et al. 2022), and various other serious chronic diseases. Specifically, ultra-processed foods such as cured meats containing added inorganic phosphates are associated with carotid intimal thickening (Itkonen et al. 2014), decreased renal function (Duong et al. 2022), and low HDL cholesterol (Fulgoni et al. 2022). Causality between phosphate additive use in ultra-processed foods and increased risk of chronic disease or mortality remains to be established. However, there is growing awareness that the use of phosphate additives in food processing increases the total phosphate availability and content of foods.

NOVA Food Classification Definitions	Representative Foods (Prepared phosphate Content:mg P/100 g)	Main Forms of phosphate	Estimated phosphate Availability (%)
Group 1. Minimally Processed, Unprocessed Foods: Natural plant and animal foods and water processed by drying, crushing, grinding, fracturing, filtering, roasting, boiling non-alcoholic fermentation, past-eurizing, refrigeration, chilling, freezing, placing in container and vacuum packaged for storage	Cooked oatmeal (99) Boiled lentils (180) Boiled black beans (140) Soy flour (674) Corn flakes breakfast cereal (58)	OPi from Plant-derived protein and phytate	<40-50%
	Baked chicken breasts (228) Baked tuna fillet (326) 2% Milk (92) Broiled beef steak (189) Boiled egg (126)	OPi from Animal-derived protein	>60-70%
Group 2. Processed Culinary Ingredients Includes oils, butter sugar, and salt that allows for preparing unprocessed foods at home	Soy oil (0) Butter (24) Sugar (0) Salt (0)	ND	ND
Group 3. Processed Foods: Foods processed by various preservation or cooking methods or fermentation as in bread and usually contains 2 to 3 ingredients.	Grilled Chicken Patty, from frozen (208) Cheddar Cheese (473) Canned Tuna* (311) Canned Green Beans* (19)	OPi from animal protein, plant protein, and phytate with use* of Pi additives	Mixed diet: >60–90%
Group 4. Ultra-processed Foods: Foods industrially formulated from substances derived from foods, additives, and ultra-processed products not usually used in home cooking such as hydrogenated oils, hydrolyzed proteins, added sugars and salt	Fried chicken nuggets*(213) Fried Sausages** (174) Fried battered fish sticks*(171) Baked from frozen pizza* (215) Processed Cheese* (982) Cheerios breakfast cereal** (448) Pancakes from Mix* (334) Commercial white bread** (109)	OPi from Animal Protein with added **IPi and OPi from additives and isolates OPi from processed Plant protein having lower phytate but higher **IPi and OPi from additives and isolates	Ultra-processed Animal foods ~90 - 100% Ultra- processed Plant foods >70 – 100%

Table 23b.3 Characteristics and sources of phosphate (organic (OPi), inorganic (IPi) or phytate) in foods classified according to degree of commercial processing. * Indicates presence of > 1 IPi additive by many top selling packaged foods. ** Indicates frequent use > 1 IPi additive + processed protein isolates or concentrate. No determination (ND) made for Group 2. Source: Modified from (Uribarri & Calvo, 2023) using NOVA system of (Monteiro et al.2017).

As can be seen in Table 23b.3, it is difficult to describe dietary sources of phosphate as high or low without information on the source and form of phosphate, and their relative bioavailability. In general, both plant and animal protein sources are good sources as noted earlier. In addition, the phytate-phosphorus present mainly in unrefined cereals, oil seeds, and legumes may become bioavailable, if during processing phytate has been hydrolyzed, and phosphate bound to phytate released prior to absorption. Under the Nova classification, raw and minimally processed phytate rich plant foods have lower phosphorus bioavailability than comparably processed animal protein sources (Calvo and Uribarri, 2021).

The presence of phosphate additives in minimally and ultraprocessed foods (shown in Table 23b.3 by *) may or may not show differences in total phosphate content compared to unprocessed foods if the content estimates are based on national nutrient content data base information (Calvo, Moshfegh & Tucker, 2014). There is a lack of accounting for the phosphorus contribution by phosphate additives in most foods in the nutrient content data bases resulting in a widely recognized underestimation of phosphorus intake (Calvo, Sherman, Uribarri, 2019). Regrettably, many investigators have only recently

discovered the need to directly analyze the phosphate content of the foods fed in studies to accurately design clinical trials examining dietary phosphate metabolism (Stremke et al. 2018).

The phosphorus content of packaged foods in the US and Canada does not require phosphorus content to be listed on the label; however, if phosphate additives were added, then their use must be identified but not quantified in the label ingredients list (Calvo, Sherman, Uribarri, 2019). The US Food and Drug Administration (FDA) requires that all ingredients (additives) added to food during processing must have prior approval for use in one of the 32 specific technical functions recognized by the FDA. Phosphate containing additives and processed protein ingredients (isolates and hydroysates) are approved for at least 26 of these technical functions. Processed foods often contain one or more phosphate additives (Sullivan et al. 2007), because the more frequently used additives are approved for more than one technical function. For example, of the more than 60 frequently used phosphate additives more than 30 are approved for use as a nutrient supplement, 24 for use as a stabilizer or thickener, 20 as emulsifiers and emulsifier salts and 18 as pH control agents. Understanding the role of dietary phosphate intake in chronic disease risk requires better understanding of the role of phosphate additives in food processing as phosphate additives can be added to foods for multiple functions, each contributing to higher phosphate content which is not always captured by the basic tools used by nutritional scientists to determine total phosphate intake. A simple solution to this inaccuracy in the nutrient content data bases is to require phosphorus content on the Nutrient Facts Label (Calvo, Sherman, Uribarri, 2019).

23b.8 Abnormalities in Serum phosphate

Phosphate balance, a proxy for assessing phosphate nutritional status, is best assessed by measuring fasting serum phosphate concentrations. Nevertheless, single fasting serum phosphate measures do not always reflect the body phosphate stores because acute shifts of phosphate between body compartments may temporarily affect serum phosphate without affecting total body phosphorus content. Clinically, patients may present with either hypophosphatemia (serum phosphate < 0.87mmol/L), or hyperphosphatemia (serum phosphate > 1.45mmol/L), with each one of these two conditions characterized by different manifestations and causes that cannot always be attributed to issues with intakes of dietary phosphate. The differences in clinical manifestations and causes for hypophosphatemia and hyperphosphatemia are summarized in Tables 23b.4 and 23b.5 (Koumakis et al. 2021).

Paths to Acute Acquired Hypophosphatemia	Causative Mechanism
Acute Shift in Extracellular to Intracellular Distribution	Refeeding syndrome Metabolic acidosis Glucose infusion and other carbohydrates Acute respiratory alkalosis Alcohol withdrawal Serious burns, surgical trauma Hyperthermia Hormonal or other agents : (insulin, glucagon, cortisol, catecholamines, fructose) Rapid cell proliferation or uptake (hungry bone syndrome, cancer)
Decreased Dietary Intake	Severe dietary restriction and malnutrition (renal failure)

Clinical manifestations of hypophosphatemia include muscle weakness, cardiomyopathy, respiratory insufficiency, osteomalacia, rickets, blood disorders, nervous system dysfunction, hypercalciuria and impaired insulin secretion. Acute hyperphosphatemia is associated with hypocalcemia, metastatic calcification, the gradual progression of renal failure, and secondary hyperparathyroidism (Uribarri & Calvo, 2023).

Paths to Acute Acquired Hypophosphatemia	Causative Mechanism
	Anorexia Kwashiorkor (severe protein / calorie malnutrition)
Decreased Intestinal Absorption	Vitamin D deficiency Antacid overuse phosphate binder use Gastrointestinal malabsorption
Increased Renal Excretion	Primary hyperparathyroidism Secondary hyperparathyroidism (dietary phosphate excess and low calcium intake or vitamin D deficiency) Metabolic acidosis (volume expansion, Fanconi syndrome, tumor production of PTH-related peptide, neurofibromatosis; acute falciparum malaria, and various medications including bisphosphonates such as etidronate, pamidronate, zoledronic acid for post-menopausal osteoporosis)

Table 23b.4 Mechanisms Causing Hypophosphatemia Data source: (Koumakis et al., 2021).

Transcellular phosphate shifts such as those occurring with acute alkalosis can produce significant hypophosphatemia by the intracellular shift of phosphate, even though the total body phosphate content is unaffected. These shifts are usually transient in nature; however, when hyperphosphatemia or hypophosphatemia are chronic, there is usually a correlation between serum phosphate levels and total body phosphate. Moreover, there is a significant circadian variation in serum phosphate concentration, as well as gender and age differences in serum phosphate unrelated to phosphate intake effect on balance. Given these problems with significant variation in serum concentration, the European Food Safety Authority (EFSA, 2015) as well as other countries did not consider serum phosphate concentration to be an appropriate biomarker for establishing dietary phosphate requirements or nutritional status. In contrast, the Institute of Medicine of North America adopted the measurement of serum inorganic phosphate as an acceptable and easy to monitor indictor for determining phosphate requirements for adults in the U.S. and Canada (IOM, 1997).

Duration of Hyperphosphatemia	Mechanism Associated with Hyperphosphatemia
Acute Hyperphosphatemia	Acute kidney injury Increased intestinal absorption of excess dietary load phosphate-containing enemas Transcellular shifts from intra to extracellular (hemolysis, rhabdomyolysis, cidosis, tumorlysis) Hyperthermia Heat stroke
Chronic Hyperphosphatemia	Chronic kidney disease Hypoparathyroidism Pseudohypoparathyroidism Vitamin D intoxication Disorders of magnesium regulation (PTH regulation) Acromegaly

Table 23b.5 Causes of Hyperphosphatemia. Data source: (Koumakis et al., 2021)

23b.9. Disease Risk Linked to Excess Dietary phosphate

High intakes of phosphate that exceed the dietary requirements or upper tolerable level, often in the absence of hyperphosphatemia, have been associated with risk of diseases such as cardiovascular disease, and higher mortality in the general population (Uribarri & Calvo, 2013; Chang et al., 2014). An imbalance in the ratio of dietary calcium to phosphate intake arising from a low calcium intake in the presence of diets containing phosphate-containing additives in ultra-processed foods, has been associated with elevated concentrations of parathyroid hormone (secondary hyperparathyroidism) (Kemi et al. 2009). Sustained secondary hyperparathyroidism can adversely impact bone formation, increasing the risk of bone fragility in advanced age. High phosphate diets also impair kidney function over time and have been shown to increase the progression to end-stage renal disease (i.e., complete kidney failure) (Zoccali et al., 2011). More recently, risk of cancer, notably prostate cancer in men, was found to be associated with high dietary phosphate (Lv et al., 2022), while studies in rodent models have reported strong evidence for risk of other types of cancer (Arnst & Beck, 2021).

A less studied disease risk of excess phosphate intakes in the general population that has been associated with hyperphosphatemia (serum phosphate ≥ 1.0, 42mmol/L) is anemia, as defined by low hemoglobin concentrations. This finding was first revealed in U.S NHANES 2005–2010 surveys, and later linked to inflammation (Wojcicki, 2013; Czaya et al., 2022). Other disease or health risks linked to high phosphate diets include accelerated aging (Kuro, 2021) and kidney stones (Khan et al. 2018). All these adverse health risks associated with excessive phosphate intakes highlight the urgent need for further research exploring how current dietary phosphate intakes may impact health and longevity.

23b.10 Inherited and Tumor-induced Disorders of phosphate Metabolism

Genetic-related disorders of phosphate metabolism , notably chronic hypophosphatemia, are very rare in most populations, Moreover, they are unrelated to dietary phosphate intakes, unlike the disorders associated with excessive phosphate intakes. These genetic phosphate disorders include X-Linked Hypophosphatemic Rickets (XLH); Autosomal-dominant Hypophosphatemic Rickets (ADHR); Autosomal Recessive Hypophosphatemic Rickets (ARHR), and Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH). They are inherited diseases or result from missense mutations which all impact FGF-23 metabolism, by either increasing circulating levels of the hormone or its activity, which ultimately lead to hypophosphatemia arising from phosphate wasting (i.e., excessive urinary phosphate excretion in relation to serum phosphate level). Sustained hypophosphatemia can manifest as rickets in children and osteomalacia in adults but can be treated with oral phosphate supplementation, and more recently with biologics that block FGF-23 renal hormone action (Athonvarangkul & Insogna, 2021).

Tumor-induced osteomalacia (also known as oncogenic osteomalacia) is also a disorder of phosphate wasting, but it is not inherited, instead stemming from excessive levels of FGF-23 secreted by tumors. Such excessive levels of FGF-23 again promote renal phosphate wasting resulting in under-mineralized bone (osteomalacia), bone pain, fractures, and muscle weakness in adults (Brandi et al. 2021).

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