Phosphorus

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Importance of phosphorus for health

Phosphorus is an essential part of all known protoplasm with a uniform content across most plant and animal tissues, with the exceptions of cells with a high ribonucleic acid or myelin content. It is most commonly present in nature as phosphate ions (PO_4^{3-}).

Phosphorus is an essential element in the human body, being part of the phospholipid bilayer of cell membranes, and acting as a structural component of bones and teeth (1). Further, phosphorus functions in critical metabolic pathways to produce and store energy in the adenosine triphosphate (ATP) molecule (1, 2), it buffers the pH of the blood, regulates gene transcription, activates the catalytic activity of enzymes and permits signal transduction for regulatory pathways affecting several organ functions from renal excretion to the immune response (1, 3). Since these reactions do not consume phosphorus indefinitely, the function of dietary phosphorus intake is to support tissue growth, and to replace losses due to growth and excretion (3).

Tissue phosphorus concentration ranges from about 7.8 to 20.1 mg (0.25-0.65 mmol) per g protein (3), and phosphorus makes up about 1% of total body weight (1). About 80% of the phosphorus component of an adult body is held in bone as hydroxyapatite, with the rest distributed through the soft tissues (4). Phosphorus is the main component of phospholipids, which make up most biological membranes, in addition to nucleotides and nucleic acids. In whole blood, most of the phosphorus is in this form, phospholipids of red blood cells, though about 3.1 mg/dl is present as inorganic phosphate (3). Though this is <1% of total body phosphorus, this fraction is critical: for example, osteoblasts require a critical level of inorganic phosphate in the extracellular fluid surrounding these cells for proper functioning, and a depletion impairs osteoblast function and limits mineral deposition in bone (3).

Dietary phosphorus exists as a mixture of inorganic and organic forms, the organic form being hydrolysed by intestinal phosphatases so that most phosphorus is absorbed as inorganic phosphate. This mainly occurs by a passive, concentration-dependent process, however a portion of dietary phosphorus is absorbed via an active transport system facilitated by 1,25-dihydroxyvitamin D. Phosphorus homeostasis is maintained in adults by keeping urinary excretion equivalent to net absorption, with equal amounts deposited and resorbed from bone (1). Regulation is achieved via a complex relationship between bone, kidney and the intestine (1). Phosphorus concentrations are regulated alongside those of calcium by vitamin D, PTH and FGF23.

Phosphorus is widely available in many foods, and bioavailability is generally good, though from plant sources, it may be limited by being present as a complex with phytic acid. Some colonic bacteria can hydrolyse phytic acid, thereby liberating the phosphorus, as can yeasts, thus leavened bread products have a higher phosphorus bioavailability than unleavened bread (3). Phytic acid can also complex with other mineral ions in the intestine e.g. calcium and zinc, which not only blocks the absorption of these minerals, but blocks the hydrolysis of phytate, thereby interfering with the liberation and subsequent absorption of phosphorus (5). This may explain why calcium can inhibit phosphorus uptake. Otherwise, despite much past literature on the ratio of calcium and phosphorus in the diet, a review concluded that there is little evidence that this ratio is important during most of life (3).

Risks of inadequate phosphorus intake

Dietary phosphorus deficiency is rare due to the wide availability of phosphorus in the diet and mechanisms in the body to conserve phosphorus. Risk of deficiency is greater with anorexia or alcoholism, and other physiological disorders including genetic disorders and those related to tumours (1). Dietary phosphorus absorption is reduced by aluminium-containing antacids and pharmacologic doses of calcium carbonate (though ingestion within normal recommendations does not interfere with phosphorus absorption) (3).

Depletion of phosphorus leads to low circulating phosphorus (hypophosphatemia) and low urinary phosphorus excretion. Because of the close relationship between calcium and phosphorus excretion, chronically low phosphorus can lead to rickets in children and osteomalacia in adults,

however such phosphopenic rickets is usually due to genetic or renal disorders affecting phosphate reabsorption (6).

Risks of excessive phosphorus intake

The risk of excessive phosphorus intake in the modern diet is greater than the risk of inadequacy. The extent and usage of phosphate salts as additives has increased substantially. Phosphates are used for moisture retention, smoothness and binding (3), rather than for a nutritive function. Phosphate intakes may be substantial in those consuming a diet reliant on processed foods, and with a high consumption of cola beverages.

Analysis of the US NHANES III dietary data revealed an association between high dietary phosphorous consumption and increased risk of all-cause mortality in healthy US adults with a normal kidney function (7). The elevated phosphorus intake corresponding to adverse effects occurred at a threshold of 1400 mg P/day. Though this equates to twice the US recommended daily allowance, over one-third of Americans reported consuming >1400 mg P/day, indicating a potentially important public health problem (7).

Elsewhere in the literature, elevated serum phosphorus levels have been associated with indicators for cardiovascular disease (8), though much of the literature to date is mainly focused on subjects with concomitant kidney disease, and epidemiologic data linking dietary phosphorus intake in healthy adults and morbidity or mortality due to cardiovascular disease are too weak to form conclusions (9).

Human biomarkers of phosphorus status

In the circulation, only a small proportion (~10%) is present as inorganic phosphorus bound to proteins. The remainder is present as inorganic phosphates and it is this fraction that is measured using typical analytical methods.

Serum phosphate

Serum phosphorus is useful in a clinical setting but is not an ideal biomarker for population studies, because the concentration is efficiently controlled within a relatively narrow range in healthy adults and it is influenced by many factors including age, sex and time since last meal (9). Further, studies show that there is no clear relationship between phosphorus and diet (9).

Serum phosphate may be measured in lithium heparin plasma or serum. EDTA citrate, and oxalate plasma should not be used. Haemolysis should be avoided because of the relatively high phosphorus content of red blood cells. Delay in separation of plasma/serum may increase phosphate levels and therefore samples should be spun within 1 hour of collection.

Serum phosphate is most often measured in the investigation and monitoring of hypophosphataemia, e.g. in critically ill patients, those at risk of re-feeding syndrome or

after treatment for diabetic keto-acidosis. It is also used in the investigation and monitoring of hyperphosphataemia, e.g. in chronic kidney disease (CKD) or in conditions resulting in cell death, and as part of the investigation of disorders of calcium homeostasis.

Urinary phosphate

Urine samples should be fresh or acidified to reduce the formation of insoluble calcium phosphate complexes. Excretion of phosphorus is via the kidneys, and parathyroid hormone and FGF-12 adjust renal clearance (3). A 24 h collection may be taken to reduce the effect of diurnal variation and diet on phosphate excretion (although is subject to inaccuracy arising from problems with collection) (10).

Urine phosphate is most often measured together with serum phosphate, and urine and serum creatinine, to enable calculation of the renal tubular reabsorption of phosphate (TmP/GFR), which can be used to investigate the cause of hypophosphataemia. See http://www.acb.org.uk/Nat%20Lab%20Med%20Hbk/Phosphate.pdf For more details**.**

Methods

Details of both serum/plasma and urinary phosphate can be found from the UK Association of Clinical Biochemistry (2012), here:
http://www.acb.org.uk/Nat%20Lab%20Med%20Hbk/Phosphate.pdf

Other phosphorus biomarkers

Recent research cites fibroblast growth factor-23 and Klotho may show promise as biomarkers of phosphorus status and metabolism (8).

Accreditation schemes

For laboratory accreditation, validation and details on availability of proficiency testing, please see the OpeN-Global page on Laboratory accreditation: https://open-global.kcl.ac.uk/accreditation/

Technical assistance

Please contact the OpeN-Global team via www.open-global.kcl.ac.uk/contact/

Useful links

Chang AR, Lazo M, Appel LJ, Gutierrez OM, Grams ME 2014 High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III. Am J Clin Nutr **99**:320-327, available here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4177334/

UK Association of Clinical Biochemistry Methods of phosphate analysis, available here:
http://www.acb.org.uk/Nat%20Lab%20Med%20Hbk/Phosphate.pdf

Further reading

Abuduli M, Ohminami H, Otani T, Kubo H, Ueda H, Kawai Y, Masuda M, Yamanaka-Okumura H, Sakaue H, Yamamoto H, Takeda E, Taketani Y 2016 Effects of dietary phosphate on glucose and lipid metabolism. Am J Physiol Endocrinol Metab 310:E526-538.

Calvo MS, Uribarri J 2013 Public health impact of dietary phosphorus excess on bone and cardiovascular health in the general population. Am J Clin Nutr 98:6-15.

de Boer IH, Rue TC, Kestenbaum B 2009 Serum phosphorus concentrations in the third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis 53:399-407.

Dominguez JR, Kestenbaum B, Chonchol M, Block G, Laughlin GA, Lewis CE, Katz R, Barrett-Connor E, Cummings S, Orwoll ES, Ix JH, Osteoporotic Fractures in Men Study Research G 2013 Relationships between serum and urine phosphorus with all-cause and cardiovascular mortality: the Osteoporotic Fractures in Men (MrOS) Study. Am J Kidney Dis 61:555-563.

Haap M, Heller E, Thamer C, Tschritter O, Stefan N, Fritsche A 2006 Association of serum phosphate levels with glucose tolerance, insulin sensitivity and insulin secretion in non-diabetic subjects. European journal of clinical nutrition 60:734-739.

Khattab M, Abi-Rashed C, Ghattas H, Hlais S, Obeid O 2015 Phosphorus ingestion improves oral glucose tolerance of healthy male subjects: a crossover experiment. Nutr J 14:112.

References

1. Calvo MS, Lamberg-Allardt CJ 2015 Phosphorus. Adv Nutr **6**:860-862.

2. Kraft MD 2015 Phosphorus and calcium: a review for the adult nutrition support clinician. Nutr Clin Pract **30**:21-33.

3. US Institute of Medicine. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Chapter 5, Phosphorous. https://www.ncbi.nlm.nih.gov/books/NBK109813/. (Last accessed on 23 August, 2018).

4. Bonjour JP 2011 Calcium and phosphate: a duet of ions playing for bone health. Journal of the American College of Nutrition **30**:438s-448s.

5. Lee HH, Loh SP, Bong CF, Sarbini SR, Yiu PH 2015 Impact of phytic acid on nutrient bioaccessibility and antioxidant properties of dehusked rice. J Food Sci Technol **52**:7806-7816.

6. Prentice A 2013 Nutritional rickets around the world. The Journal of Steroid Biochemistry and Molecular Biology **136**:201-206.

7. Chang AR, Lazo M, Appel LJ, Gutierrez OM, Grams ME 2014 High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III. Am J Clin Nutr **99**:320-327.

8. Park W, Kim BS, Lee JE, Huh JK, Kim BJ, Sung KC, Kang JH, Lee MH, Park JR, Rhee EJ, Oh KW, Lee WY, Park CY, Park SW, Kim SW 2009 Serum phosphate levels and the risk of cardiovascular disease and metabolic syndrome: a double-edged sword. Diabetes Res Clin Pract **83**:119-125.

9. Gutierrez OM 2013 The connection between dietary phosphorus, cardiovascular disease, and mortality: where we stand and what we need to know. Adv Nutr **4**:723-729.