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Serum phosphate in older people

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Summary

Phosphate (PO_4^-) has a number of important functions in the human body and abnormalities of phosphate handling and phosphate levels are common in older people. We review the physiological functions of phosphate, the effects of phosphate deficiency and excess, and discuss the evidence underpinning management of these conditions in older people. Both hyper- and hypophosphataemia have been associated with a variety of adverse effects in different patient groups. There is currently little evidence to guide practice in treatment of abnormal phosphate levels specifically in older people. Studies looking into the effect of replacing phosphate on morbidity and mortality in milder cases of hypophosphataemia and into the dangers of, and treatment of, hyperphosphataemia in older people are required.

Keywords: Hypophosphataemia, hyperphosphataemia, aged.

Introduction

The mineral phosphorous in the form of phosphate (PO_4^-) has a number of important functions in the human body, and is the major intracellular anion. It is integral to many core biochemical processes in the body, but is often not measured in clinical practice. Nevertheless, abnormalities of phosphate handling and phosphate levels are common in older people and are clinically important in some cases. We review the physiological functions of phosphate, the effects of phosphate deficiency and excess, and discuss the evidence underpinning management of these conditions in older people.

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Physiology

Phosphate plays a vital role in cellular energy transfer in the form of adenosine triphosphate (ATP), and is part of important co-enzymes such as nicotinamide adenine dinucleotide phosphate (NADP). Phosphate plays a part in intracellular signalling by forming second messengers such as inositol 1,4,5-triphosphate (IP_3), which in turn signals release of calcium from intracellular stores, and adenosine 3′,5′-cyclic monophosphate (cAMP) and guanosine 3′,5′-cyclic monophosphate (cGMP). It is vital for nucleic acid synthesis and, as part of 2,3 diphosphoglycerate (DPG), it shifts the oxygen dissociation curve to the right, thus increasing oxygen delivery to peripheral tissues. It acts as an important intracellular buffer against acid–base challenges. Because of these functions, phosphate is necessary for the normal function of red blood cells, leucocytes, platelets, oxygen release from oxyhaemoglobin, muscle cell function and the central nervous system. As part of the mineral matrix in bone and as a component of phospholipids, phosphate also plays a major structural role in bone and in all cell membranes.

Phosphate metabolism and regulation

Total body phosphate normally amounts to about 700 g, the majority (80%) of which is in bone, bound to calcium. Most of the rest is contained intracellularly (mainly in myocytes) and only a small proportion of total body phosphate is found in the extracellular space. The total amount of phosphate in the body, and the proportion in different body compartments, depends on a number of factors: intake, intestinal absorption, renal excretion, the shift of phosphate into and out of cells from the blood, and bone metabolism. Rapid changes in serum phosphate usually reflect redistribution between the extracellular and intracellular pools. Phosphate behaves in a

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similar way to potassium in that it enters cells in association with glucose, a process driven by insulin. Alkalosis also drives phosphate into cells in exchange for hydrogen ions. Slower changes in serum phosphate levels are often the result of changes in intake, absorption, excretion and bone metabolism. In bone, phosphate forms part of calcium hydroxyapatite: in addition to its major structural role here it also forms the major storage pool for both calcium and phosphate from which these minerals can be mobilized, if required, to maintain serum levels. As a result, changes in serum phosphate are often accompanied by a corresponding change in serum calcium level, which has separate, but complementary, clinical effects.

Intake and absorption

Meat and dairy products are major dietary sources of phosphate. Diet usually contains an adequate or more than required amount of phosphorus. About 60–70% of dietary phosphate is typically absorbed. Intake of phosphate may not be low in older people, and absorption of phosphorus is reduced to a lesser extent with advancing age than absorption of calcium. In fact, calculation of nutrient intake of Swiss women aged 75–87 years showed that intake of phosphate was almost 70% higher than the recommended nutritional requirement.[1] Maximum absorption of phosphates occurs in the jejunum by both active and passive processes. Transepithelial transport across the intestinal epithelium is driven by an active sodium-dependent process via type II sodium phosphate co-transporters (NaPi-II), which are expressed in the apical membrane.

Renal excretion

Under steady state, the urinary excretion of phosphate equals the dietary absorption. About 70% of the phosphate filtered at the glomeruli is reabsorbed in the proximal tubules and only 30% is excreted. The maximal tubular reabsorptive capacity is therefore the main determinant of renal phosphate loss and is determined by the level of expression of similar sodium phosphate co-transporters (NaPi-I and NaPi-II) as found in the jejunum. Factors that reduce renal phosphate reabsorption are parathyroid hormone (PTH), intravascular volume expansion, hypercalcaemia and fibroblast growth factor-23 (FGF-23). The main physiological role of PTH is to increase serum calcium levels, but as it works by stimulating breakdown of calcium hydroxyapatite in bone it also releases phosphate. The effect of PTH on the kidneys is therefore primarily a physiological mechanism to prevent a related rise in serum phosphate. Factors that increase renal phosphate reabsorption are parathyroidectomy, volume depletion, hypocalcaemia, growth hormone, insulin and insulin-like growth factor (IGF-1). IGF-1 levels have been found to be lower in older people[2] and this may be a factor contributing to the lower serum phosphate levels found with ageing.

Serum levels and changes with age

Serum phosphate levels are said to be 'normal' if they are within a range of 0.8–1.4 mmol/l. This may not necessarily reflect phosphate content at the intracellular level, which is where many of its functions occur. Serum assays measure inorganic orthophosphates, 10% of which are bound to proteins, 5% are complexed with calcium and magnesium and 85% are $H_2PO_4^-$ and HPO_4^{2-}. An Italian study showed that serum phosphate levels decrease with age in men and women except for a transient increase in women during the perimenopausal period.[3] They showed that, as stated above, this was mainly due to a decrease in the tubular reabsorption with age. This reduction in tubular absorption may be mediated by low vitamin D levels that are common in older people.[4] Low vitamin D levels lead to secondary hyperparathyroidism, with a consequent reduction in renal phosphate absorption. However, it is also well known that chronic kidney disease (CKD) leads to higher serum phosphate levels. The prevalence of renal disease due to vascular disease and diabetes is high in older people, and it would be expected that these effects may counteract the effects of reduced tubular phosphate reabsorption in some patients.

It should also be noted that serum phosphate level gives no indication of the total body stores, as it only makes up a small proportion of our total phosphate. As the serum level is so tightly regulated, patients could have a total body deficit of phosphate but maintain a normal serum level. Conversely, shifts of phosphate

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between compartments could lead to a low serum phosphate level while total body stores are maintained.

Hypophosphataemia

Incidence, mechanisms and risk factors

Various studies have reported the prevalence of hypophosphataemia (usually defined as a serum phosphate less than 0.8 mmol/l) in hospital patients as between 2 and 43%. The incidence appears especially high in intensive care and infectious disease units.[4–6] Two studies have examined the incidence of hypophosphataemia specifically in older people. One case control study enrolled patients aged 65 or over who were admitted to the geriatric division of a community hospital.[7] The most common reasons for admission to the hospital were sepsis (defined as positive blood cultures), infection, respiratory exacerbation (asthma, COPD or congestive cardiac failure), malignancy, fractures, and stroke. The study found that 14.1% of patients admitted over a 1 year period had at least one documented episode of hypophosphataemia (defined as a serum phosphate of 0.77 mmol/l or less). Severe hypophosphataemia (phosphate $\leq$0.45 mmol/l) was found in 4.1% of patients. Significantly more patients with hypophosphataemia reported weight loss of greater than 5% in the 3 months prior to admission than those who did not have hypophosphataemia. Sepsis and infection were the most common reasons for admission in the hypophosphataemia group. Serum phosphate at admission was within the normal range and levels reached a nadir at mean of 11 days following admission. Hypophosphataemic patients also had significantly lower serum albumin, potassium and calcium levels and were more likely to have received intravenous fluids (particularly glucose-containing solutions) and/or nutritional supplementation, including enteral tube feeding, during their admission.

A study of very old women (mean age 86 years) admitted to a specialist geriatric admissions ward in the UK found that 29% (27/96) of patients had at least one episode of hypophosphataemia (defined as phosphate <0.8 mmol/l).[8] Two of these had moderate hypophosphataemia (<0.5 mmol/l) and none had severe hypophosphataemia (<0.32 mmol/l). The authors found that hypokalaemia, active cancer, low body mass index (BMI), receipt of intravenous fluids and the use of laxatives were independently associated with hypophosphataemia.

Refeeding syndrome

Many of the risk factors for developing hypophosphataemia overlap with those factors known to increase the risk of refeeding syndrome.[7,8] This syndrome often occurs on a background of preceding depletion of lean body mass and total body phosphate, magnesium and potassium. Serum levels of these electrolytes are typically maintained during the starving phase, but when a carbohydrate load is ingested, insulin is released in response, and phosphate, magnesium and potassium shift from the extracellular compartment to the depleted intracellular compartment, causing a rapid fall in serum electrolyte levels. The change in the serum electrolyte levels may also result in significant fluid shifts, and a lack of dietary cofactors, particularly thiamine, may exacerbate the metabolic sequelae of these electrolyte shifts. The clinical consequences of abnormal levels of potassium are particularly detrimental and widespread. Abnormalities impair nerve and muscle (including myocardium) depolarization, thus precipitating arrhythmias, heart failure and muscle weakness. It can cause delirium and coma and the risk of infections increases. These are all common clinical problems in older people so the complex clinical syndrome can become difficult to diagnose.

The typical patient with refeeding syndrome is acutely ill, has had poor oral intake over several days to weeks, has ongoing poor nutrition risk and is given glucose-containing fluids while in hospital.[9,10] In a study of critically ill patients in an intensive care unit (mean age 65 years) it was found that starvation for as little as 48 hours could predispose to moderate to severe hypophosphataemia during refeeding and significantly increase length of mechanical ventilation and hospitalization.[11] In this study, hypophosphataemia developed much earlier (after 1.9 days on average) than in the patients on the geriatric ward in the study described above.[8] Older people could be considered especially at risk for refeeding as a significant proportion have one or more risk factors.[8] Refeeding syndrome may therefore account for some of

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the hypophosphataemia seen in older people. However, older hypophosphataemic patients may only share common risk factors with those who develop refeeding syndrome, and there is as yet no proof that this is the mechanism for hypophosphataemia in this group.

Sepsis

As with younger patients, sepsis seems to be a predominant risk for development of hypophosphataemia in older people, with fever and increased white cell count both having been shown to be independent predictors.[7] One study found that 42% of septic patients had at least one phosphate value below the reference level, and the presence of hypophosphataemia was associated with increased C-reactive protein levels and white blood cell counts.[5] The authors of this study suggest that the common risk factor of malnutrition leading to both an increased risk of severe infection and hypophosphataemia may be responsible for this association. The catabolic state and increased insulin release caused by sepsis may also play a part, as may the increased loss of phosphate (along with magnesium and potassium) via the kidneys associated with the late phase of the febrile period.[12] The fall in phosphate may reflect a shift of phosphate intracellularly, which is where the ion is required for so many biochemical processes. The level of serum phosphate may not directly have adverse consequences, but may reflect a greater need for phosphate inside the cells of a very metabolically active patient.

Consequences of hypophosphataemia

Severe hypophosphataemia has been associated with a number of adverse pathological and physiological effects including rhabdomyolysis, haemolysis, myocardial depression leading to left ventricular dysfunction, skeletal muscle weakness, impairment of white blood cell function and decreased insulin sensitivity.[13] It is also known to cause seizures and decreased consciousness. Case report evidence suggests that correction of hypophosphataemia can reverse these problems.[14,15] Furthermore, hypophosphataemia has been associated with increased morbidity and mortality in intensive care units,[16] patients with respiratory tract infections,[17] older patients[7,8] and patients with severe sepsis.[18] Patients (mean age 63 years) admitted to surgical and medical wards and found to be hypophosphataemic were shown to have decreased respiratory muscle function which improved to the level of that found in normophosphataemic patients with repletion of phosphate.[19]

Whereas previously it was thought that only moderate to severe degrees of hypophosphataemia had a clinical impact, recent evidence suggests that, in older people, even a mild degree of hypophosphataemia, which is often asymptomatic and only discovered incidentally, is associated with markedly increased mortality.[8] It may be that mild hypophosphataemia is an epiphenomenon; it may merely indicate frailty and a malnourished state which itself leads to greater mortality rather than the low phosphate level itself.

Phosphate replacement

Supplementation with phosphate-containing compounds has been shown to improve respiratory muscle function in patients with COPD.[20,21] Any effect on cardiac function remains contentious, with human studies showing conflicting results.[13] We found no studies supporting a role for phosphate replacement in improving white cell function or insulin sensitivity. It is not known, at present, whether treating milder degrees of hypophosphataemia in the elderly will improve prognosis.

If supplemental phosphate is given, it is usually in the form of either oral potassium phosphate (25–50 mg/kg/day in divided doses or 0.8–1.6 mmol/kg/day), increasing phosphate in nasogastric or parenteral feeds or intravenous replacement. Oral replacement can cause diarrhoea when given in high doses so, if the deficit is large, intravenous replacement is often preferred. Hypophosphataemia may occur in critically ill patients despite giving nutritional formulae with supplemental phosphorus by the enteral or parenteral route.[11] Although a dose of 50 mmol of intravenous phosphate over 24 hours was found to be safe in a general ward setting,[22] many guidelines recommend monitoring for cardiac arrhythmias. Careful monitoring of electrolytes is required to prevent hyperphosphataemia and hypocalcaemia, as the response to replacement is highly variable between individuals. A few

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protocols have been described to guide the rate of replacement of phosphate based on serum levels and body weight, but these were delivered in a general adult population in a surgical intensive care unit and a tertiary care institution in critically ill patients, so may not be directly translatable to an older population in a non-critical care ward setting.[23,24]

It is preferable to try to avoid hypophosphataemia developing in the first place. Those at risk of refeeding syndrome and developing hypophosphataemia need to be recognized, and should have feeding started slowly. Calorific intake should be increased gradually while monitoring and replacing electrolytes as appropriate. Patients who are significantly hypophosphataemic should have serum phosphate normalized before commencing feeding, especially if enteral tube feeding or parenteral nutrition is to be undertaken. A study of patients receiving parenteral nutrition concluded that the initial amount of infusion should be no more than 70% of the patient's calculated requirements.[10] This study also showed that the initial 24 hours infusion should contain at least 12 mmol of phosphate.

It is important to remember that, in patients with resistant hypophosphataemia, one should look for malignancy, especially paraproteinaemias, as some assays may report spurious low phosphate levels in these conditions.

Hyperphosphataemia

Causes

Hyperphosphataemia is usually associated with excessive phosphate ingestion, impaired renal excretion (due to renal failure or abnormal PTH action on renal tubules), increased release from the intracellular compartment, or a combination of these factors. Increased phosphate intake does not necessarily have to be due to dietary intake or oral supplements; there are a number of case reports of hyperphosphataemia resulting from phosphate laxatives, enemas and bowel preparations in older people.[25–27] Those who appear to be especially susceptible are patients with renal impairment, those who are dehydrated (a common side-effect of phosphate laxatives), and those with impaired bowel motility. The commonly encountered combination of decreased gut motility and decreasing renal function in older people may be responsible for the increased risk of hyperphosphataemia in this situation. One study of 70 patients aged 25–80 years found that serum phosphate levels were significantly higher following ingestion of phosphate-containing colon cleansing agents and the mean change in phosphate level was positively correlated with age.[28] Older people were found to be at risk of hyperphosphataemia despite normal creatinine clearance rates and serum creatinine levels.

Consequences of hyperphosphataemia

The deleterious effects of a rise in serum phosphate levels are mediated as much by the corresponding fall in calcium level as by the high phosphate itself. Therefore, high phosphate can cause a decreased conscious level, coma, tetany, convulsions, laryngeal spasm, itch and cardiac arrhythmias, among other consequences.

Cardiovascular effects

Hyperphosphataemia can cause precipitation of calcium in tissues such as the walls of blood vessels, thus reducing their compliance. This may explain why a high serum phosphate has been shown to be an independent cardiovascular risk factor, predicting mortality and morbidity in a variety of patient groups including those with type 2 diabetes,[29] those with a history of myocardial infarction,[30] and those without known cardiovascular disease.[31–33]

The problem of hyperphosphataemia in patients with renal failure, and its implications, has long been recognized. These patients are therefore the most studied group with regard to the effects and management of hyperphosphataemia. Recently, there has been some interest in the adverse effect of hyperphosphataemia in patients without renal impairment. In patients with known coronary artery disease, higher phosphate levels, even within the normal range, were associated with an increased death and cardiovascular event rate.[30] In younger people without previous cardiovascular problems, those with high normal phosphate levels had a higher incidence of cardiovascular disease when followed up for 20 years.[31] Possible mechanisms for this are increased vascular risk due to inhibition of vitamin D synthesis,[34,35] tendency to vascular calcification, subclinical renal

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dysfunction and higher PTH levels – all known to be associated with increased vascular risk. Other studies have reported that low phosphate levels are also associated with cardiovascular disease, while higher levels are associated with death and stroke.[32] Serum phosphate levels in patients without renal impairment may have a biphasic effect in that high levels are associated with cardiovascular risk factors, whereas low serum phosphate levels are associated with the metabolic syndrome which is itself associated with cardiovascular mortality and morbidity.[36] The association between hypophosphataemia and the metabolic syndrome may be related to a low dietary intake of phosphorous, and thus may just be a marker of an unhealthy diet that itself contributes to the metabolic syndrome.[37]

It is possible that the differences observed between studies are a result of gender differences. An increased degree of atherosclerosis has been reported in men, but not in women, with high normal phosphate levels at baseline.[38] The reason for this gender difference has not been explained. The subjects of this study were aged 45–64 years, which encompasses the normal age of menopause. It is possible that the slight increase in phosphate that has been shown to occur transiently in the perimenopausal period[3] (as outlined in the introduction above) has been detected. This transient elevation of phosphate may not be sufficient to have as much of a detrimental effect as a more prolonged period of hyperphosphataemia.

It should be noted that almost all the studies summarized above were performed in young or middle-aged adults. No studies have focused on the over-75s and only a few included patients aged over 65. Therefore their direct applicability to typical older frail patients is questionable. Additionally, as all these papers were from observational data, they can show only an association rather than proving that it is hyperphosphataemia *per se* that causes adverse outcomes. So, should we treat hyperphosphataemia in the elderly and, if so, how should we do this? There is very little evidence to guide practice in this area. It might be expected that reducing oral phosphate intake would be beneficial in hyperphosphataemia; however, one study has found that in patients on haemodialysis who are prone to hyperphosphataemia, lowering phosphorus intake may actually increase mortality.[39] This may have occurred because the harmful effect of the associated fall in protein intake outweighed the benefit of the fall in phosphate.

Bone metabolism

Hyperphosphataemia exerts an influence on bone metabolism and strength. An excess of phosphate in the extracellular tissues can cause hypocalcaemia which, along with reduced production of 1,25 vitamin D (due to renal dysfunction), can lead to increased PTH levels. This combination of derangements leads to bone demineralization and increased fracture risk. Even in those without renal dysfunction, increased oral intake of protein and phosphorus has been associated with increased renal loss of calcium, higher PTH, reduced calcitriol and increased bone resorption.[40] Phosphate from different foods affects bone resorption differently. An observational study in younger women found that phosphate from additives in processed foods may have greater negative impact on PTH levels than phosphorus from other food sources.[41] One study of patients over the age of 40 years has estimated that the risk of fractures increases by 9% for every 100 mg increase in phosphate intake.[42] Many of the subjects in this study were malnourished in other bone-related nutrients; thus adverse effects on bone metabolism may not be the same as in an otherwise healthy population. Older people may be at a high risk for high phosphate-induced fractures as they commonly have other nutritional risk factors. However, as with many of the studies on cardiovascular risk outlined above, studies have been carried out in younger patients who we already know have different bone metabolism to older people.

Conclusion

Older people are at risk of both hypo- and hyperphosphataemia. There appears to be a greater risk of hypophosphataemia developing compared with hyperphosphataemia, and evidence from studies involving frailer older patients suggests that this is associated with adverse outcomes.

There is currently little evidence to guide practice in treatment of abnormal phosphate levels in older people, with most guidance coming from extrapolating results of studies in younger people and those with renal failure. It seems reasonable

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to give phosphate supplementation if serum phosphate is <0.5 mmol/l. The development of hypophosphataemia in patients at risk of refeeding syndrome is a common clinical problem and early involvement of dieticians is critical in detecting and managing the syndrome. It is still unclear whether treating hyperphosphataemia is beneficial at all in terms of reducing cardiovascular risk and how it is best to go about this.

Studies looking into the effect of replacing phosphate on morbidity and mortality in milder cases of hypophosphataemia are required. This may indicate if there is a causal relationship between low serum phosphate levels and mortality, and whether it should be treated with supplementation. There is also a need for studies looking at the effects and possible treatments for hyperphosphataemia in older people, as opposed to younger patients or those with renal failure. Such studies need to examine the effect on quality of life and gastrointestinal side-effects, as well as on bone health, cardiovascular parameters, muscle strength, length of hospitalization and mortality.

Conflicts of interest

The authors declared no conflicts of interest.

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