

Phosphate (serum, plasma, urine)

1 Name and description of analyte

1.1 Name of analyte

Phosphate

1.2 Alternative names

Phosphorus, inorganic phosphorus (Pi), PO_4 .

1.3 NMLC number

1.4 Description of analyte

Phosphates are inorganic salts of phosphoric acid containing the group PO_4^{3-} . In the body, the major species of inorganic phosphate are HPO_4^{2-} and H_2PO_4^- ; in most body fluids (the urine is an exception) the ratio $[\text{HPO}_4^{2-}]:[\text{H}_2\text{PO}_4^-]$ is $\sim 4:1$.

1.4 Function of analyte

Phosphate is structurally important in bones and teeth where it is combined with calcium in the form of hydroxyapatite. It is a component of nucleic acids, nucleotides, phospholipids and of many enzymes. Phosphate is vital for energy metabolism, muscle contraction, nerve signalling, intracellular signalling and electrolyte transport. Phosphate is an important buffer, particularly in the urine and contributes to the maintenance of acid-base status.

2 Sample requirements and precautions

2.1 Medium in which measured

Serum or plasma (lithium heparin); concentrations may be 0.06 to 0.10 mmol/L lower in heparinised plasma than in serum. There are also indications for measuring phosphate in urine.

Anticoagulants such as EDTA, citrate, and oxalate can interfere with the formation of the phosphomolybdate complex in the standard analytical method.

2.2 Precautions re sampling, handling etc.

1. Haemolysis can cause an artefactual increase in [phosphate] (by approximately 30%).
2. [Phosphate] may also be increased by a prolonged delay in separation of serum or plasma from cells.
3. Urine samples should be fresh or acidified to reduce the formation of insoluble calcium phosphate complexes. 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). If the sample is to be used for calculation of renal tubular reabsorption of phosphate (TmP/GFR), it should be taken into a plain bottle, fasting, together with a serum sample, to allow simultaneous measurement of serum phosphate, and urine and serum [creatinine](#).

3 Summary of clinical uses and limitations of measurements

3.1 Uses

Serum phosphate is 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
- in the investigation and monitoring of hyperphosphataemia, e.g. in chronic kidney disease (CKD) or in conditions resulting in cell death
- as part of the investigation of disorders of calcium homeostasis.

Urine phosphate is 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.

3.2 Limitations

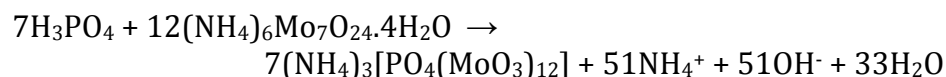
Measurement of serum phosphate does not provide information as to the cause of either hyper- or hypophosphataemia.

Serum [phosphate] does not necessarily reflect intra-cellular [phosphate].

4 Analytical considerations

4.1 Analytical methods

1. All routine methods use the reaction of phosphate ions with ammonium molybdate under acidic conditions. This produces a phosphomolybdate complex that is measured by spectrophotometry, either directly at 340 nm, or, following reduction to molybdenum blue, at 600 to 700 nm.



A number of reducing agents have been used, including aminonaphtholsulphonic acid, ferrous ammonium sulphate, stannous chloride, ascorbic acid and semidine hydrochloride.

2. Other methods for measurement of phosphate include vanadate-molybdate and enzymatic methods.

4.2 Reference method

There is no official reference method; however, an ammonium molybdate method using semidine hydrochloride as the reducing agent has been published as a 'Selected Method' by the American Association for Clinical Chemistry.

4.3 Reference materials

There is no official reference material.

4.4 Interfering substances

Haemolysis or delayed separation of cells from serum/plasma can cause an artefactual increase in [phosphate] (by approximately 30%). This is due to the formation of inorganic phosphate by the action of phosphatases on organic phosphates, both of which are released from

damaged red cells. Lipaemic or icteric samples may also give erroneous results. Mannitol, fluoride and monoclonal proteins (particularly IgM) have been reported to interfere.

4.5 Sources of error

The phosphomolybdate reaction is robust but pH must be controlled as both complex formation and the reduction of molybdate are pH-dependent.

5 Reference intervals and variance

5.1.1 Reference interval (adults)

Serum/plasma: 0.8–1.5 mmol/L

Urine: 13–42 mmol/24 h

TmP/GFR: 0.80–1.35 mmol/L

5.1.2 Reference intervals (others)

Serum/plasma:

neonates (<4 weeks) 1.3–2.6 mmol/L

infants (4 weeks– <1 year) 1.3–2.4 mmol/L

children (1–16 y) 0.9–1.8 mmol/L

lactation 1.1–1.5 mmol/L

TmP/GFR (children) 1.15–2.44 mmol/L

5.1.3 Extent of variation

5.1.3.1 Interindividual CV

Serum/plasma: 9.4%

Urine (concentration): 26.5%

5.1.3.2 Intraindividual CV

Serum/plasma: 8.5%

Urine (concentration): 26.4%

5.1.3.3 Index of individuality

Serum/plasma: 0.90

Urine: 0.63

5.1.3.4 CV of method

Typically <2.0%

5.1.3.5 Critical difference

Serum/plasma: 27%

Urine: 54%

5.1.4 Sources of variation

1. Age: serum [phosphate] is highest in early infancy, gradually decreasing through childhood and adolescence to adult values. A decline in serum [phosphate] is seen in adult men after the age of 40.
2. Lactation: serum [phosphate] is higher during lactation.
3. Diurnal variation: serum [phosphate] reaches a nadir between 8.00 and 11.00 am.
4. Prandial status: serum [phosphate] rises postprandially and then falls. Measurement of fasting concentrations is recommended.
5. Urine phosphate excretion varies with age, time of day, renal function, plasma [PTH], muscle mass and diet. Renal tubular reabsorption of phosphate (TmP/GFR) is considered to be a better measure of renal phosphate handling.

6 Clinical uses of measurement and interpretation of results

6.1 Uses and interpretation

1. Investigation and monitoring of hypophosphataemia, e.g. in critically ill patients, those at risk of re-feeding syndrome, or after treatment for diabetic ketoacidosis. Mild hypophosphataemia (0.48–0.80 mmol/L) is not uncommon in hospitalised patients and may resolve with the underlying cause or oral supplementation. Lower serum [phosphate] will require treatment to prevent organ dysfunction and rhabdomyolysis. Chronic hypophosphataemia may be as a result of a hereditary condition (one of various types of renal phosphate wasting) and requires further investigation.
2. Investigation and monitoring of hyperphosphataemia, e.g. in chronic kidney disease (CKD), or in conditions resulting in cell death e.g. tumour lysis syndrome. Renal failure is the most common cause of hyperphosphataemia. A rapid increase in plasma [phosphate] can result in hypocalcaemia.
3. Investigation of disorders of calcium homeostasis
In hypercalcaemia secondary to hyperparathyroidism, serum [phosphate] is usually decreased. In hypercalcaemia of malignancy, serum [phosphate] may be elevated (although not invariably).
4. Urine phosphate is 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. A low TmP/GFR is found in several disorders of renal phosphate handling that result in hyperphosphaturia, hypophosphataemia and osteomalacia.

6.2 Confounding factors

Diurnal variation and prandial status can affect serum [phosphate].

7 Causes of abnormal results

7.1 High values (serum/plasma)

7.1.1 Causes

1. Pseudohyperphosphataemia (haemolysis, paraprotein).
2. Increased phosphate load
 - oral, intravenous or rectal phosphate supplementation
 - vitamin D intoxication
 - cell death (tumour lysis syndrome, rhabdomyolysis, malignant hyperthermia)
 - transcellular shift (lactic acidosis, respiratory acidosis, diabetic keto-acidosis).
 - renal failure (acute, chronic)
3. Decreased renal phosphate excretion
 - hypoparathyroidism
 - acromegaly
 - bisphosphonate therapy.

7.1.2 Investigation

The cause of hyperphosphataemia may often be clinically apparent. Measurement of serum sodium, potassium, urea, [creatinine](#) and [calcium](#) should be undertaken. Dependent on these results and the clinical presentation, measurement of serum/plasma magnesium, PTH, 25-hydroxycholecalciferol and [glucose](#) and blood gas analysis also be useful.

Measurement of serum total protein, and haemolysis index may help to exclude pseudohyperphosphataemia.

7.2 Low values (serum/plasma)

7.2.1 Causes

1. Intracellular shift

- re-feeding syndrome
- recovery from diabetic ketoacidosis
- respiratory alkalosis
- sepsis
- oral/intravenous glucose
- insulin.

2. Decreased intestinal absorption

- vomiting
- diarrhoea
- excess antacids
- malabsorption
- malnutrition
- vitamin D deficiency.

3. Increased renal phosphate excretion

- hyperparathyroidism
- disorders of renal phosphate handling (e.g. Fanconi's syndrome, hypophosphataemic rickets, oncogenic osteomalacia).

7.2.2 Investigation

The cause of hypophosphataemia may often be clinically apparent. Basic investigations are as for hyperphosphataemia. Calculation of TmP/GFR can be useful in chronic hypophosphataemia to determine whether it is secondary to excess renal loss.

7.3 Notes

Severe hypophosphataemia (<0.32 mmol/L) requires prompt treatment to prevent widespread organ dysfunction. This may be with oral or, if necessary, intravenous phosphate. Serum [phosphate] and [calcium] should be monitored during treatment. Pre-treatment with phosphate supplements may be appropriate for patients at risk of re-feeding syndrome.

8 Performance

- 8.1 Sensitivity, specificity etc. for individual conditions
Not applicable

9 Systematic reviews and guidelines

9.1 Systematic reviews

Many reviews have been published. Most look at hyperphosphataemia in CKD, or hypophosphataemia in the critically ill. For example:

1. Palmer SC, Hayen A, Macaskill P *et al.* Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in Individuals with Chronic Kidney Disease. *JAMA* 2011;305:1119-1127. *The authors conclude that there appears to be an association between higher serum [phosphate] and mortality in*

patients with CKD.

2. Geerse DA, Bindels AJ, Kuiper MA *et al.* Treatment of hypophosphatemia in the intensive care unit: a review. *Crit Care* 2010;14:R147. *The authors found that there was some evidence that hypophosphatemia was associated with higher mortality in critically ill patients; however, there was a lack of robust evidence demonstrating whether correction of hypophosphatemia improves outcomes.*

9.2 Guidelines

1. CG73 Chronic kidney disease: NICE guideline 73. September 2008
<http://guidance.nice.org.uk/CG73/Guidance/pdf> (accessed 8.v.2012)
This guideline recommends the measurement of serum [phosphate] in patients with CKD stage 4 and 5.
2. UK Renal Association Clinical Practise Guideline: CKD-Mineral and Bone Disorders (CKD-MBD). December 2010.
http://www.renal.org/whatwedo/news/10-12-22/Final_version_of_RA_Clinical_Practice_Guideline_CKD-Mineral_and_Bone_Disorders_CKD-MBD.aspx (accessed 8.v. 2012)
This guideline advises on the monitoring of serum [phosphate] in CKD stages 3-5, and gives target concentrations.
3. CG32 Nutrition support in adults: NICE guideline. February 2006.
<http://guidance.nice.org.uk/CG32/Guidance/pdf> (accessed 8.v.2012)
This guideline advises on the measurement and replacement of phosphate prior to introduction of nutritional support in those considered at risk of re-feeding syndrome, and also the frequency with which serum [phosphate] should be monitored during re-feeding.

9.3 Recommendations

The following articles provide a general overview of phosphate homeostasis, and discuss causes, investigation and treatment of hyper- and hypophosphataemia:

1. Weisinger JR, Bellorin-Font E. Magnesium and phosphorus. *Lancet* 1998;352:391-396.
2. Moe MS. Disorders involving calcium, phosphorus, and magnesium. *Prim Care* 2008;35:215-237 *This article provides an overview of the use of TmP/GFR*
3. Payne RB. Renal tubular reabsorption of phosphate (TmP/GFR): indications and interpretation. *Ann Clin Biochem* 1998;35:201-206.

10 Links

10.1 Related analytes

None

10.2 Related tests

Serum phosphate may be measured as part of the investigation into disorders of calcium homeostasis, together with analytes including serum [calcium](#), [creatinine](#), alkaline phosphatase activity, magnesium, PTH and 25-hydroxycholecalciferol.

Urine and serum phosphate may be measured with urine and serum [creatinine](#) to enable calculation of the renal tubular reabsorption of

phosphate (TmP/GFR), which may be used to determine whether hypophosphataemia is due to renal loss of phosphate.

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