

Parathyroid hormone (serum, plasma)

1 Name and description of analyte

1.1 Name of analyte
Parathyroid hormone (PTH)

1.2 Alternative names
Parathormone

1.3 NMLC code

1.4 Description of analyte

PTH is an 84-amino acid linear peptide hormone (MW ~9500 Da). It is synthesised as a larger precursor (115 amino acids); the removal of a chain of 25 amino acids produces pro-PTH from which removal of a further six amino acids produces PTH. It is secreted exclusively by the parathyroid glands. The principal stimulus to secretion is a low ionised [calcium], which is sensed by a calcium-sensing receptor located on the plasma membrane of parathyroid cells. Secretion is inhibited by an increased ionised [calcium]. Secretion is also reversibly inhibited by severe hypomagnesaemia.

The parathyroids also secrete fragments of PTH, and hepatic and renal metabolism of the hormone also result in the appearance of fragments of PTH in plasma. Normally, only 10–20% of the overall immunoreactive forms of PTH detectable in the plasma comprise the intact form. Only the intact hormone and some N-terminal fragments have biological activity; the ability of immunoassays also to detect inactive fragments (some of which have long half-lives) has been a major problem in the use of PTH assays.

1.5 Function of analyte

The major actions of PTH are to:

- reduce the reabsorption of phosphate in the proximal tubules
- increase the reabsorption of calcium in the distal tubules
- stimulate the activity of 25-hydroxy vitamin D3 1 α -hydroxylase (EC 1.14.13.13), the enzyme responsible for the generation of calcitriol (which in turn stimulates the absorption of dietary calcium from the gut)
- stimulate osteoclastic bone resorption.

In the kidneys, PTH also decreases the proximal reabsorption of bicarbonate. Overall, therefore, the actions of PTH tend to raise plasma [calcium]; it may also induce a mild hyperchloraemic acidosis. It causes hypercalciuria because of the higher filtered load of calcium, despite the increased reabsorption.

2 Specimen requirements and precautions

2.1 Medium in which measured

PTH is typically measured in serum or EDTA plasma; values in EDTA plasma tend to be up to 20% lower than in serum from the same blood sample.

- 2.2 Precautions re sampling, handling etc.
1. PTH is labile; serum or plasma should be separated as soon as possible. EDTA tubes must be filled to capacity. Separation should ideally take place in a refrigerated centrifuge. Specimens may be stored at 2–8 °C for up to 8 h before analysis, but for longer storage should be frozen.
 2. [PTH] shows some diurnal variation and it is recommended that samples are obtained in the morning, preferably after an overnight fast.
 3. No other special precautions apply.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

PTH measurements are used:

1. in the differential diagnosis of hypercalcaemia
2. in the differential diagnosis of hypocalcaemia
3. in the localisation of source of increased PTH production (using selective venous sampling)
4. to assess the completeness of parathyroid surgery (typically intra-operatively using a dedicated point-of-care (PoC) analyser)
5. in the monitoring of patients with chronic kidney disease.

3.2 Limitations

The results of PTH measurements are highly assay-dependent (see section 4.1).

4 Analytical considerations

4.1 Analytical methods

PTH is measured by immunoassay.

1. First generation (radioimmuno-) assays were introduced in 1959 and were in use until 1987; they used a single antibody directed against C-terminal epitopes and measured many fragments as well as the intact hormone. They should be regarded as obsolete.
2. Second generation (immunometric) assays (so-called 'intact assays') were introduced in 1987. They use two antibodies, one specific for a C-terminal amino acid sequence and one for an N-terminal sequence (sandwich assay). They were thought to measure only intact PTH but they have been demonstrated to measure large (amino acids 7–84) fragments that can inhibit the binding of PTH to its normal (PTH1) receptor and bind to a specific C-terminal receptor present in various tissues (e.g. skin and haemopoietic system as well as bone), but with unknown function.
3. Third generation assays (so-called 'whole PTH assays') were introduced in 2000. They use a more restricted N-terminal antibody and were believed to measure only intact PTH although there is evidence that they react to a form of PTH called amino-PTH that has been identified in some patients with parathyroid carcinoma and severe hyperparathyroidism.

4.2 Reference method: none.

4.3 Reference material: none (assays are generally standardised against purified human PTH and validated by comparison with other assays and by clinical utility).

4.4 Interfering substances
Lipaemic, haemolysed or icteric samples may give erroneous results.

4.5 Sources of error
The presence of heterophilic antibodies *in vivo* can cause *in vitro* interference with PTH assays but does not appear to be a major problem. As with all assays, and immunoassays in particular, results must be interpreted in relation to clinical and other laboratory data.

5 **Reference intervals and variance** (*data presented are for second generation ('intact') assays*).

5.1.1 Reference interval (adults): typically 1.3 – 6.8 nmol/L but assay-dependent

5.1.2 Reference intervals (others): no major differences except in the immediate neonatal period, when concentrations tend to be higher.

5.1.3 Extent of variation

5.1.3.1 Interindividual CV 43.4%

5.1.3.2 Intraindividual CV 25.4%

5.1.3.3 Index of individuality 0.58

5.1.3.4 CV of method: approximately 5%

5.1.3.5 Critical difference 72%

5.1.4 Sources of variation

PTH secretion is increased in vitamin D deficiency (secondary hyperparathyroidism). It is known that sub-clinical vitamin D deficiency is common (prevalence in some studies up to 50% of the adult population at the end of the winter months). This reciprocal co-dependence makes it difficult to define a true upper reference limit for [PTH].

[PTH] increases slightly with age, but it is unknown whether this is a primary effect of aging or a reflection of vitamin D status.

6 **Clinical uses of measurement and interpretation of results**

6.1 Uses and interpretation

1. Hypercalcaemia

Since PTH secretion is inhibited by hypercalcaemia, the detection of PTH in hypercalcaemic individuals (even if the result is within the reference interval) suggests autonomous secretion (hyperparathyroidism); if PTH is undetectable, it may be inferred that a non-parathyroid cause is responsible.

2. Hypocalcaemia

Hypoparathyroidism is a rare cause of hypocalcaemia; if parathyroid function is intact, [PTH] is elevated by hypocalcaemia (unless there is accompanying hypomagnesaemia). A low [PTH] in a hypocalcaemic patient implies impaired parathyroid function (although note that [PTH] is typically elevated in pseudohypoparathyroidism).

3. Localisation of source of PTH

A high ratio of [PTH] in a sample drawn from a specific vein to [PTH] in plasma from peripheral blood suggests that the vein is draining a source of PTH.

4. Intraoperative monitoring

Because PTH has a short half-life, a rapid fall in [PTH] is expected after removal of a source of increased secretion. Failure of a fall to occur suggests the presence residual tissue secreting PTH. *Note that to be fully effective this requires PoC testing using a dedicated instrument.*

5. Monitoring chronic kidney disease (CKD)

PTH accumulates in chronic kidney disease, owing to reduced catabolism of the hormone. This can have an adverse effect on bone metabolism in CKD patients. The Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines recommend regular measurement of [PTH] in CKD patients, the value being maintained within target ranges depending on the CKD stage (e.g. 3.5–7.0 pmol/L for stage 3; 7.0–11.0 pmol/L for stage 4; 15–30 pmol/L for stage 5).

6. PTH measurements have been used to indicate cut-off points for the diagnosis of vitamin D insufficiency, on the grounds that even sub-clinical deficiency may increase PTH secretion (secondary hyperparathyroidism) (see 5.1.4 and 9.1). PTH measurements should not be used routinely to diagnose vitamin D insufficiency.

6.2 Confounding factors

As has been stressed, [PTH] results are assay-dependent. When monitoring individual patients' [PTH] results, the same assay should be used.

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

High values occur in:

- primary hyperparathyroidism (whether caused by adenoma(s), parathyroid hyperplasia or carcinoma)
- secondary hyperparathyroidism (typically secondary to vitamin D deficiency and in chronic kidney disease)
- tertiary hyperparathyroidism (typically in patients with previous CKD-related secondary hyperparathyroidism post transplant)
- chronic kidney disease (see 7.3)
- pseudohypoparathyroidism.

7.1.2 Investigation

[PTH] is measured as part of the investigation of other conditions and high values should not otherwise be encountered. Imaging and selective venous blood sampling can be used to locate the source of increased PTH secretion.

7.2 Low values

7.2.1 Causes

Low values occur in:

- hypoparathyroidism
- hypercalcaemia of non-parathyroid origin, e.g. in malignancy due to secretion of parathyroid-related peptide by a tumour.

7.2.2 Investigation

PTH is measured as part of the investigation of other conditions and low values should not otherwise be encountered.

7.3 Note

In CKD, [PTH] may be increased in part as a response to a tendency to hypocalcaemia (secondary hyperparathyroidism) and in part secondarily to decreased catabolism of the hormone.

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

Numerical data are of limited value because of assay variation. However, elevated [PTH] has been shown to *predict* high turnover bone disease in patients with chronic kidney disease on replacement treatment, and a risk of hypocalcaemia (and thus for treatment with vitamin D) in patients following total thyroidectomy.

9 Systematic reviews and guidelines

9.1 Systematic reviews

1. Responses of parathyroid hormone to vitamin D supplementation: a systematic review of clinical trials. Björkman M, Sorva A, Tilmis R. Archives of Gerontology and Geriatrics 2009;48:160-166.
This review of 52 published studies concludes that although serum PTH concentrations decline with vitamin D supplementation at any initial serum 25-OHvitamin D concentration, because of confounding factors, PTH measurements should be interpreted with caution in the context of the assessment of the adequacy of vitamin D supplementation.

9.2 Guidelines

1. Clinical knowledge summaries. Hypercalcaemia: management; interpreting PTH levels.
http://cks.nhs.uk/hypercalcaemia/management/scenario_diagnosis_and_assessment#451265006 (accessed 8.v.2012)
This guideline provides guidance on the interpretation of measurements of PTH concentrations in patients with hypercalcaemia.

2. Lamb EJ, Vickery S, Ellis AR. Parathyroid hormone, kidney disease, evidence and guidelines. Annals of Clinical Biochemistry 2007; 44:1-4.
This short review examines the use of PTH measurements in chronic kidney disease and concludes that 'second generation' assays (see 4.1 (2)) are not fit to be used with current guidelines. See also 9.3.

3. Intraoperative parathyroid hormone. Laboratory medicine practice guidelines: evidence-based practice for point-of-care testing. Sokoll LJ, Remaley AT, Sena SF *et al.* Intraoperative parathyroid hormone. In: Laboratory medicine practice guidelines: evidence-based practice for point-of-care testing. Washington (DC): National Academy of Clinical Biochemistry (NACB); 2006. pp.105-119.
This guideline recommends the use of PoC parathyroid hormone measurements in all first time surgery for primary hyperparathyroidism (especially using minimally invasive techniques), for re-operation and for localisation using radiologically-guided selective venous sampling.

9.3 Recommendations

Parathyroid hormone measurement in CKD. Souberbielle J-CP, Roth H,

Fouque DP. *Kidney International* 2010;77:93-100.

This article reviews the role of PTH measurements in monitoring CKD, including their value and potential pitfalls.

10 Links

10.1 Related analytes

Parathyroid hormone-related peptide is a 141-amino acid peptide responsible for the majority of the cases of humoral hypercalcaemia of malignancy. It has eight N-terminal amino acids in common with PTH and binds to the PTH receptor. It can be measured by immunoassay but in practice it is rarely necessary to do so.

10.2 Related tests

Measurement of PTH is usually prompted by the finding of hyper- or hypocalcaemia. Other investigations that may be of value in investigating disorders of calcium homeostasis include serum phosphate, creatinine, magnesium, alkaline phosphatase activity and 25-hydroxycholecalciferol (vitamin D).

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