The Parathyroid Glands, Primary and Secondary Hyperparathyroidism and Assays for Parathyroid Hormone

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Background

The four parathyroid glands are bean-sized organs found in the neck near the thyroid gland. These glands synthesize parathyroid hormone (PTH or parathormone) which helps the body to use and store calcium and to maintain the calcium levels in the blood within normal limits. Actually, as far as we know, the only role of PTH is in calcium homeostasis.

Hyperparathyroidism exists when a parathyroid gland becomes overactive and produces too much PTH. This can occur when an adenoma (a non-cancerous growth) forms on one of the parathyroid glands causing it to grow and become overactive. Roughly three in 10,000 persons are affected by primary hyperparathyroidism (PHP). Much more common is secondary hyperparathyroidism (SHP) which is a result of kidney disease. SHP becomes more prevalent as the kidney output declines and calcium is retained by the system.

In the outpatient population, SHP is one of the more common causes of hypercalcemia. “Stones, bones, and groans” is the medical-school mnemonic that summarizes the primary manifestations of hypercalcemia, which often leads to kidney stones, accelerated bone loss, and gastrointestinal discomfort; only about 15 percent of patients with hypercalcemia have any symptoms. While many patients with PHP have no symptoms, the classical features of PHP include a history of kidney stones, fragility fractures, and osteoporosis. Hyperparathyroidism is unusual in children, unless they have kidney disease. In many cases the diagnosis of HPT is made after a diagnosis of thyroid disease. The diagnosis of PHP in pediatric patients is frequently delayed, is commonly asymptomatic, and has significant morbidity. For children in whom PHP is suspected, evaluation of serum calcium and PTH levels is diagnostic in 100% of children; more often the PTH levels will be increased even when the serum calcium or ionized calcium levels are ‘normal.’

Parathyroid resection is effective at restoring normal serum calcium, has few complications, and is the treatment of choice for children and adults with primary hyperparathyroidism.

As mentioned SHP is usually the direct cause of renal disease and is caused by hypocalcemia, hyperphosphatemia and vitamin D deficiency. A PTH assay is the best test for SHP.

As mentioned many patients with PHP have no symptoms. When they exist they include the following:

- Weakness.
- Feeling very tired.
- Nausea and vomiting.
- Loss of appetite.
- Weight loss for no known reason.
- Constipation.
- Being much more thirsty than usual.
- Trouble thinking clearly.
- Urinating much more than usual.

Once blood tests are done and PHP is diagnosed, imaging tests may be done to help find which of the parathyroid glands is overactive. Sometimes the parathyroid glands are hard to find and imaging tests such as those listed below are done to find exactly where the glands are.

- Sestamibi scan
- CT scan (CAT scan)
- Ultrasound exam
- Angiogram

Certain factors affect prognosis and treatment options. The prognosis and treatment options depend on the following:

- Whether the calcium level in the blood can be controlled.
- The stage of the cancer.
- Whether the tumor and the capsule around the tumor can be completely removed by surgery.
- The patient’s general health.

Assays of PTH in the treatment of PHP and SHP and in monitoring SHP.

To discuss the utility of PTH assays, it is necessary first to review the structure of PTH and its major metabolites and the assay methods themselves.

PTH is a polypeptide hormone consisting of 84 amino acids which take a rather convoluted three dimensional shape. For the sake of simplicity we have drawn it here as simply as long chain:
There are three types of assays, from several vendors; are all sandwich assays using a capture Ab (Abc) and a signal Ab (Ab s). These sandwich the PTH between them (Abc -PTH- Abs) by binding at different sites on the amino acid chain. It is these binding sites that separate one assay from another and that have led to some discussion about the validity and utility of the assays.

We can divide the assays into three generations:

1. These assays have some cross-reactivity with N-terminal fragments and over-estimate the amount of biological PTH. The over-estimation can be as high as 40 - 160% if an antibody which reacts with aa7-aa84 is used. These are rarely if ever used today.

2. In these assays there is no cross reactivity with aa1-aa84 (These are also called bio-intact, iPTH, whole PTH, and PTH (1-84).

3. These use aa1-aa4 and aa1-aa84 antibodies. They are not yet commercially available on automated systems. There is a significant variation in assay results between different manufacturers. This is due to the use of: different epitopes and a lack of standardization.

The table below gives the commercially available assays using automation and the epitopes they recognize.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Epitope of Coated Ab</th>
<th>Epitope of labeled Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPC</td>
<td>44-84</td>
<td>1-34</td>
</tr>
<tr>
<td>Bayer</td>
<td>39-84</td>
<td>1-34</td>
</tr>
<tr>
<td>Roche</td>
<td>26-32</td>
<td>55-64</td>
</tr>
<tr>
<td>Tosoh</td>
<td>39-84</td>
<td>1-34</td>
</tr>
<tr>
<td>Allegro</td>
<td>39-84</td>
<td>1-34</td>
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With this as background, we continue with a series of abstracts for the current literature directed at the utility of PTH assays to detect both PHP and SHP. Many of the assays discuss the use of intraoperative measurement of PTH (IOPTH). The advantages of this approach are that it essentially ensures the surgeon that all diseased tissue has been removed (in PHP).

One study involved 345 consecutive patients with PHP and positive localization studies for a single parathyroid adenoma. One group of 157 patients underwent parathyroid exploration without PTH testing; a second group of 188 patients had an operation with PTH testing. Of the first group, 10% still were hypercalcemic postoperatively. In contrast, among the 188 person group 2 patients, 170 (90%) had resection of a single parathyroid adenoma, a greater than 50% decrease in PTH levels, and were cured. The remaining 18 patients did not have an adequate reduction in PTH levels and underwent bilateral neck exploration with resection of additional parathyroids. Of these 18 patients, 9 had double adenomas and 9 had 3- or 4-gland hyperplasia. Importantly, all patients in group 2 were cured. “PTH testing improves cure rates in patients undergoing minimally invasive parathyroidectomy. PTH testing allowed intraoperative recognition and resection of additional hyperfunctioning parathyroids missed by preoperative imaging studies.”

Parathyroid hormone (PTH) measurements serve as probably the best noninvasive, diagnostic tool for the assessment of renal osteodystrophy (i.e., SPH) . Since there are more patients who are candidates for parathyroid surgery with SHP than PHP, we looked at a number of articles regarding PTH assays in these patients. For example, in a series of 95 consecutive patients who underwent total parathyroidectomy and IOPTH measurement for renal HPT (SHP), IOPTH was measured before and 15 minutes after parathyroidectomy. At follow-up, 96% patients presented with normal calcium levels. Persistent renal HPT was seen in three patients, and recurrent HPT was diagnosed in one other patient. In 99% of the patients, the levels declined more than 50%; in 73%, the PTH decay was more than 90%. IOPTH measurement with a decrease in IOPTH of at least 90% is highly predictive of successful parathyroidectomy and normalization of postoperative calcium and PTH levels. Note that the criterion for successful surgery was not the amount of PTH following tissue removal, but the percent change in PTH.

The National Kidney Foundation guidelines for PTH levels and GFR are given in Table 1 (see following page).

In another study of SHP, blood samples were taken at baseline, within 10 min after resection and subsequently at various intervals. The range of PTH levels were 69-842 before, and 5-184 after surgery PHP, 416-1655 and 53-440 SHP. All patients but one had a significant percentage decline from pre-excision values, approximately 76% in all types of parathyroidism.

PTH in 80 patients with SHP was measured at the time of anesthesia, after dissection before resection, and 20 and 40 minutes after resection. Follow-up ranged from 3 to 24 months. Twenty minutes after resection, PTH levels remained elevated. At 40 minutes, a decrease of more than 50% of the pre-surgery level...
TABLE 1: Life Style NKF / K-DOQI: National Kidney Foundation / Kidney-Dialysis Outcome Quality Initiative

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR Range (ml/min./1.73 m2)</th>
<th>I- PTH Target Range</th>
<th>Ca / P Target Range</th>
<th>Intact PTH Target Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30-59</td>
<td>Every 12 Months</td>
<td>Every 12 Months</td>
<td>35-70</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Every 3 Months</td>
<td>Every 3 Months</td>
<td>70-110</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or dialysis</td>
<td>Every 3 Months</td>
<td>EveryMonth</td>
<td>150-300</td>
</tr>
</tbody>
</table>

The NKF/K-DOQI Guidelines are derived from studies that used the Allegro Intact PTH Assay.

References
6. Intraoperative intact parathyroid hormone determination as a predictive factor of hyperparathyroidism resolution Gomez-Pulaclos A, Taibo MA.
8. Do intraoperative total serum and ionized calcium levels, like intraoperative intact PTH levels, correlate with cure of hyperparathyroidism? Quinones RM, Pesce CE, Djuricin G.
10. Ann Surg. 2005 Sep;242(3):375-80; A comprehensive evaluation of perioperative adjuncts during minimally invasive parathyroidectomy: which is most reliable? Chen H, Mack E, Starling JR.
11. Section of Endocrine Surgery, Department of Surgery, The University of Wisconsin Medical School, Madison, WI 53792, USA. chen@surgery.wisc.edu

Intraoperative parathyroid hormone assay improves outcomes of minimally invasive parathyroidectomy mainly in patients with a presumed solitary parathyroid adenoma and missing concordance of preoperative imaging. Barczynski M, Konturek A, Cichon S, Hubalewska-Dydejczyk A, Gólkowski F, Huszno B.

indicates a ‘cure,’ which occurred in 96% of the patients.

There is an on-going discussion of how best to detect then monitor patients with increased PTH due to renal failure. There are data suggesting some fragments may appear preferentially in these patients and that some assays may not identify these patients as readily and specifically as others. There is no accord on this at present.

There have been some publications that include measurement of either or both total serum or ionized calcium at baseline and during or shortly after excision of tissue. Here the accuracy of monitoring intraoperative total and ionized Ca to that of PTH for predicting surgical cure during parathyroidectomy was determined on a group of 47 patients. The mean baseline PTH level dropped by 70% at 5 minutes after removal of the abnormal glands and by 83% at 10 minutes Total Ca decreased below baseline at 5 minutes and remained below baseline at 10 minutes in only 37 patients (79%). Ionized Ca decreased below baseline at 5 minutes and remained below baseline at 10 minutes in only 35 patients (77%). “Although inexpensive and readily available, monitoring the intraoperative ionized Ca and total Ca is not clinically reliable for confirming removal of hyperfunctioning parathyroid glands.”

With rapid, simple assays that can be performed near patient or in a core lab, the utility of PTH assays should increase. Researchers at the Washington University School of Medicine, for example, studied an experimental group of patients for whom intraoperative rapid PTH assays were between $55 and $113. Comparing this group with a historical control group, the researchers found significantly fewer frozen sections, shorter hospital stays, greater use of local anesthesia, and more unilateral rather than bilateral neck explorations.

Authors’ note: In preparing this short article, we studied quite a number of articles on PTH methods and the value of them to the clinician. Should wish a larger set of summaries please contact David at david-plaut@yahoo.com
Questions for STEP Participants

Answer questions only on the official STEP answer sheet. If you do not have the official STEP answer sheet, a year’s supply can be obtained (at no cost), simply by writing to: STEP Program Answer Sheets, American Medical Technologists, 10700 W. Higgins Road, Rosemont, IL 60018, or by fax: 847/823-0458, or by e-mail: paula.simoncini@amt1.com.

In addition to marking your answers, be sure to include all the required information on the answer sheet and a processing fee of $3.00 per article.

In the following, choose the one best answer for each question.

1. Parathyroid hormone is responsible for maintaining the levels of _______ in the bloodstream.
   A. T3 and T4
   B. TSH
   C. calcium and phosphorus
   D. iron

2. Hypercalcemia does not lead to
   A. kidney stones
   B. accelerated bone loss
   C. increased bone production
   D. gastrointestinal discomfort

3. Parathyroid disease always affects both the parathyroid glands.
   A. True
   B. False

4. The number of patients with hyperparathyroidism with symptoms is
   A. less than 20%
   B. more than 20%
   C. more than 40%
   D. more than 60%

5. PTH assays are best described as
   A. Ab1-Ab2-Ag
   B. Ag-Ab1-Ab2
   C. Ab1-Ag-Ab2
   D. Ag1-Ab-Ag2

6. Assays for PTH measure only the 1-84 amino acid chains.
   A. True
   B. False

7. A drop of PTH levels of ____ may be considered a ‘cure.’
   A. <20 units within 20 min
   B. >20 units within 20 min
   C. <50% change within 20 min
   D. >50% change within 20 min

8. In addition to PTH assays, the following have been found useful.
   A. Total calcium assays
   B. Ionized calcium assays
   C. Both total and ionized calcium assays
   D. Neither total and ionized calcium assays

9. If the intraoperative PTH does not indicate a ‘cure,’ it is most likely that
   A. the patient does not have primary hyperthyroidism.
   B. the patient has a parathyroid cancer.
   C. another sample should be drawn after 2 hours.
   D. not enough tissue has been removed.

10. The incidence of primary hyperparathyroidism increases with decreasing GFR.
    A. True
    B. False