Parathyroid Surgery in Renal Failure Patients

Vidas Dumasius, MD, Peter Angelos, MD, PhD*

Many patients with renal failure present with symptoms associated with chronically elevated levels of phosphate. In particular, the high parathyroid hormone (PTH) levels in patients with renal failure can be a management challenge. Given the unique physiologic state of these patients, their hyperparathyroidism (HPT) warrants special considerations for selecting appropriate medical and surgical management.

Secondary HPT is caused by any condition associated with a chronic depression in the serum calcium level because low serum calcium leads to compensatory overactivity of the parathyroid glands. Renal failure is, by far, the most common cause of secondary HPT, although other diseases, including inadequate dietary calcium intake, steatorrhea, and vitamin D deficiency can also cause this condition. Chronic renal insufficiency is associated with impaired phosphate excretion, which leads to hyperphosphatemia. Elevated serum phosphate directly depresses serum calcium levels and thereby stimulates parathyroid gland activity.

In contrast, tertiary HPT is observed in patients with renal failure that have undergone renal transplantation but still overproduce PTH. This condition is typically observed after successful renal transplantation when asymptomatic elevated calcium levels are observed. Laboratory studies in these patients are similar to patients with primary HPT, namely elevated PTH secondary to over activity of the parathyroid glands.

In renal HPT, the hypercalcemia is observed with elevated synthesis of calcitriol. The persistent hyperphosphatemia, bone resistance, and change in the PTH set point lead to the diffuse hyperplasia of the parathyroid glands. These changes are not limited to a single gland, but affect all of the glands.

* Corresponding author.
E-mail address: pangelos@surgery.bsd.uchicago.edu

University of Chicago Medical Center, 5841 South Maryland Avenue, MC 4052, Chicago, IL 60637, USA

doi:10.1016/j.otc.2010.01.010
0030-6665/10/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
It has been reported that 1% to 28% of patients who have hemodialysis develop significant secondary HPT.\textsuperscript{1–3} For patients with renal transplant, failure of the resolution of the calcium and phosphate metabolism leading to tertiary HPT has been estimated to occur in 1% to 10%.\textsuperscript{4,5}

CALCIUM METABOLISM

Plasma calcium exists in ionized and protein bound phases. Normally about 1gm of calcium in the inorganic form is absorbed daily in the proximal small intestine. Extracellular calcium is constantly being exchanged with that in the bone, intracellular fluid, and glomerular filtrate. Normal kidney can reabsorb 99% of the calcium that is present in the filtrate. Bone is an enormous reservoir of calcium.

The serum calcium level is controlled by the interaction of PTH, calcitonin, and Vitamin D. Vitamin D is not one molecule but a mix of sterols. Active form of Vitamin D results from activity of renal 1α-hydroxylase conversion of 25-Vitamin D to 1,2-dihydroxycholecalciferol, which is the active form of the Vitamin D. The role of the Vitamin D activity in calcium homeostasis is directed at increased intestinal absorption and increased bone resorption. As the glomerular filtration rate decreases, renal production of 1,2-dihydroxycholecalciferol decreases, leading to decreased intestinal calcium absorption to create a negative calcium balance. A compensatory increase in PTH secretion keeps the serum calcium level near normal by mobilizing calcium from bone.

Renal insufficiency with continued decrease in kidney function abrogates Vitamin D effects. Furthermore, chronic elevation of phosphate in renal failure affects parathyroid gland function. With elevated serum phosphate and low active vitamin D levels, serum calcium is low, which triggers development of secondary HPT–hypertrophy of the parathyroid glands. In contrast to what is observed in primary and tertiary HPT, patients with secondary HPT have low serum calcium levels, which lead to elevated levels of PTH.

PARATHYROID HORMONE

Parathyroid hormone is a single-chain polypeptide consisting of 84 amino acids. PTH is synthesized by chief cells of the parathyroid gland. The principal actions of parathyroid hormone include an increase in

- Serum calcium and decrease in serum phosphorus levels
- Bone osteoclast and osteoblast activity
- Gastrointestinal absorption of calcium
- Renal bicarbonate excretion
- Renal hydroxylation of 25-hydroxy Vitamin D3.

The level of serum calcium in humans is under a sensitive feedback-control mechanism. Hypercalcemia reduces parathyroid hormone secretion and the formation of 1,25-dihydroxy vitamin D3 in normal healthy individuals. In cases of secondary HPT, elevated levels of phosphate lead to suppression of the calcium levels and elevation of the PTH in response to low calcium levels.

MEDICAL TREATMENT GOALS

Given that the underlying cause for secondary HPT is overstimulation of the parathyroid glands, medical management is focused on decreasing that stimulation. One of the methods to control serum hyperphosphatemia may be achieved with phosphate
binders in conjunction with dietary limits on the phosphate intake. In addition, supplemental calcium and Vitamin D may assist in achieving these goals. Calcium may also be added to patients’ dialysate on a regular basis. Despite the best management of hyperphosphatemia, a significant number of patients may develop prominent osteodystrophy. Osteodystrophy is especially common in patients that are on chronic hemodialysis because aluminum accumulates in the bones contributing to osteomalacia. Furthermore, patients may also develop ectopic calcification.

**SURGICAL INDICATIONS IN SECONDARY AND TERTIARY HPT**

The secondary HPT in the majority of renal patients on hemodialysis may not warrant surgical intervention. Thus, medical management should always be undertaken first. The symptoms that favor surgical intervention are persistent hypercalcemia, uncontrolled hyperphosphatemia, elevated alkaline phosphatase levels, and evidence of significant bone erosion on imaging or development of osteitis fibrosa cystica (OFC). The clinical finding associated with OFC may manifest as worsening bone pain and fractures. Significant discomfort is reported from persistent pruritus and development of the soft tissue calcifications. Several additional clinical findings should be taken into consideration, such as erythropoietin resistant anemia, poorly controlled hypertension, impaired myocardial perfusion, and peripheral neuropathies. Development of significant calciphylaxis (deposition of calcium in skin) should also be taken into consideration when making a decision for surgical intervention. However, elevation of the PTH alone does not warrant surgical intervention.

Table 1 summarizes some of the critical considerations in determining indications for surgery in renal failure. Although many different factors can be examined in deciding whether to operate on patients, calcium levels, alkaline phosphatase levels, and the presence of subperiosteal bone resorption are all important. As patients progress from Stage I to Stage II, they develop relative and then an absolute indication for surgery. Certainly, any patient with a diagnosis of calciphylaxis has an absolute indication for surgery.

In cases of patients that have undergone renal transplantation, additional considerations before surgery should be undertaken. Patients with asymptomatic hypercalcemia should be observed for at least a year with demonstration of persistently elevated levels of calcium before surgery is planned. Patients who develop nephrolithiasis or nephrocalcinosis as a result of the persistent elevated levels of calcium have a clear surgical indication. More urgent surgical exploration should be undertaken if patients have acute hypercalcemia in the immediate posttransplantation period that

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Indications for surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage I</td>
</tr>
<tr>
<td>Calcium mmol/l</td>
<td>Normal</td>
</tr>
<tr>
<td>Alkaline phosphatase u/l</td>
<td>Normal range 2.1 to 2.6</td>
</tr>
<tr>
<td>Hand X ray</td>
<td>Normal</td>
</tr>
<tr>
<td>Surgical indication</td>
<td>None</td>
</tr>
</tbody>
</table>

is difficult to manage by medical means or symptomatic from hypercalcemia develop-

**PREOPERATIVE CONSIDERATIONS**

As in cases of primary HPT, noninvasive localization studies may be undertaken to evaluate parathyroid glands. Sestamibi scans provide information about the location of parathyroid glands, especially when in the face of an aberrant location or ectopic parathyroid gland. Alternatively, thallium-technetium scan can be performed although the results with Sestamibi scanning alone seem to be superior. Ultrasound can be helpful in identifying abnormal parathyroid glands in the neck and can also identify thyroid pathology. It is important to identify thyroid pathology preoperatively so that if work-up, such as fine-needle aspiration, is needed before surgery it can be undertaken. Patients can be pretreated with calcitriol for several days preoperatively in an effort to reduce postoperative hypocalcemia. Intraoperative infusion of desmopressin at induction of anesthesia may help to counteract the platelet dysfunction seen in patients with renal failure. Given the complexity of medical problems and frequent significant postoperative hypocalcemia, postoperative intensive care unit management of these patients should also be considered.

**OPERATIVE PLAN**

In preparation for parathyroidectomy in patients with renal failure, the surgeon should consider several key issues. The control of the symptoms is the goal of the surgery and may be accomplished in several ways:

- Subtotal parathyroidectomy with cervical thymectomy
- Total parathyroidectomy with autotransplantation and cervical thymectomy
- Total parathyroidectomy and cervical thymectomy without autotransplantation.

Each of these surgical approaches has advantages and disadvantages that warrant further evaluation. The incidence of supernumerary parathyroid glands has been reported in the range of 6.5% to 25% and may be the cause of the persistent or recurrent HPT. Given that a significant number of supernumerary glands are located in the thymic tissue, the optimal treatment includes resection of the upper portion of the thymus in all operations for secondary HPT. This cervical thymectomy should be considered a standard part of the operation for renal HPT. Furthermore, extra parathyroid glands also can be found in the fatty tissue behind the thyroid along esophagus or along recurrent laryngeal nerves. Niederle and colleagues reported in 1992 that 11.4% of patients had supernumerary parathyroid glands found in the fatty tissue in the neck. These reports point to the importance of thorough evaluation of all thymic tissue and posterior central soft tissue for additional parathyroid glands during any parathyroid operation for secondary HPT.

The choice of whether to perform a subtotal parathyroidectomy (sPTx) or total parathyroidectomy with autotransplantation (tPTx+AT) or just total parathyroidectomy (tPTx) is best made by the individual surgeon based on the prior experience and specific patient issues. If patients have significant calciphylaxis, the mortality rate is so high that total parathyroidectomy without autotransplantation is indicated. In this circumstance, the surgeon should strive to ensure that recurrence rates are absolutely minimized and therefore all parathyroid tissue should be removed. Theoretically, in patients on dialysis who will never receive a kidney transplant, a total parathyroidectomy should also be a reasonable operation. However, because almost every
patient on dialysis may be a transplant candidate in the future, the authors advocate either sPTx or tPTx+AT in all patients with secondary HPT in need of parathyroidectomy as long as they do not have life-threatening calciphylaxis. Individual surgeon judgment should be used to make the choice between the two operations as both have pros and cons associated with them.9,10

Subtotal parathyroidectomy (sPTx) is thought by some authors to be a less radical procedure with equally effective results.11 This procedure avoids an incision in the forearm, which may be a difficult location for some patients who have had dialysis access complications. Many surgeons prefer to see a well-vascularized remnant in situ in sPTx rather than depending on autograft function. On the other hand, tPTx+AT has the benefit of making a second operation, if necessary, easier as it can be done under local anesthesia without re-exploration of the neck. Furthermore, some studies have shown a lower recurrence rate with tPTx+AT.12 With lack of convincing data to support one operation over the other, the authors recommend that the individual surgeon make the choice realizing that to be successful, the operation must be done with meticulous technique and minimal complications.

The subtotal parathyroidectomy with cervical thymectomy should include a careful bilateral exploration of the neck. A critical part of the surgery is to identify all four glands and decide which gland is the most normal looking. This strategy is the opposite of that used for most parathyroidectomies in cases of primary HPT (Fig. 1). In primary HPT, the goal is to find the abnormal gland, and frequently when performing a minimally invasive or focused parathyroidectomy, the surgeon will not look at any glands but the abnormal one. In contrast, in patients who have renal failure with HPT, the surgeon must find all the glands and identify the most normal looking gland. If an inferior gland is small and normal looking, it should be preserved. Because inferior glands are more anterior in the neck, it is preferable to preserve an inferior gland if possible. If reoperation is needed in the future, inferior glands are more readily accessible. The gland for preservation should be carefully dissected taking care to protect the vascular pedicle. A vascular clip is then placed across the gland and the distal portion resected leaving the vascularized remnant marked with the clip. The goal is to have a 40 to 80 mg vascularized remnant of the most normal looking gland. It is critical to ensure viability of this remnant before resection of additional glands. As each parathyroid gland is completely dissected, before removing the gland, the remnant is inspected to ensure viability. If at any time the remnant appears nonviable, the surgeon can choose another gland to use for a remnant or the decision can be made to perform a total parathyroidectomy and autotransplant a parathyroid. Tomi-naga and colleagues13 have suggested that in choosing the gland to leave as a remnant or for autografting, the least nodular gland should be chosen because the glands with nodular hyperplasia are more likely to grow. In either subtotal parathyroidectomy or total parathyroidectomy with autotransplantation, cryopreservation can be undertaken with close follow-up of patients’ calcium status with excellent results achieved with delayed transplantation of the parathyroid tissue.

In cases where total parathyroidectomy with autotransplantation is being undertaken, the surgeon should initially identify all four parathyroid glands. Once this is done, the most normal-appearing and least-nodular gland should be chosen for autotransplantation. The glands for autotransplantation should be minced into approximately 1 × 2 mm pieces. A pocket should be made in brachioradialis muscle away from arteriovenous fistulae and 20 to 30 pieces of parathyroid should be autotransplanted.14,15 The autotransplant pocket should be closed with a “figure of 8” stitch and then the knot marked with a vascular clip so that the pocket could be readily found again if needed. Alternatively, parathyroid autografts can be placed in the
subcutaneous fat in the arm. If there is any concern for viability of the transplant, then cryopreservation of at least one parathyroid gland should be performed.

ADDITIONAL PERIOPERATIVE CONSIDERATIONS

At the completion of the parathyroid gland resection, several considerations should be thought through before leaving the operating room. One consideration is the decision about whether to place a cervical drain at the completion of the surgical procedure. Although no data shows that closed tube drainage of the parathyroidectomy wound reduces the likelihood of developing a neck hematoma, the authors continue to use a drain in patients with renal failure undergoing parathyroidectomy because these patients will need hemodialysis in the perioperative period. All such patients will require hemodialysis and they all will get some heparin during dialysis. Patients should be dialyzed with minimum heparin after a parathyroidectomy in the early postoperative period. Drains may be left for close monitoring over the first 24 to 48 hours with removal before the patient is discharged from the hospital. An additional consideration

Fig. 1. Differences in surgical algorithms for parathyroidectomy.
in the operating room is whether parathyroid hormone levels should be checked intraoperatively. A rapid drop in PTH levels intraoperatively is seen in patients after parathyroidectomy for primary HPT. In patients with renal failure, the speed with which PTH levels drop is reduced and controversy continues to exist at this time regarding how to best interpret the intraoperative PTH results. Nevertheless, most surgeons find knowledge of a significant drop in intraoperative PTH to be valuable in the operating room. Postoperatively, calcium levels are maintained as close as possible to normal range. Patients receive oral supplementation of the calcium and vitamin D, but for refractory cases or patients that experience symptoms of hypocalcemia (peri-orbital, hand tingling, numbness) a calcium drip may be initiated. Additionally, arrangements are made with hemodialysis services that may provide further assistance with regulation of electrolyte disbalances in renal patients. For example, in patients who are hypocalcemic, hemodialysis is performed with a high calcium bath.

SUMMARY

Treatment of HPT in patients with renal failure is a complex surgical issue. Given the multitude of medical problems that patients with renal failure have, a diligent selection of the patients that should undergo surgical intervention must be undertaken. Furthermore, no single optimal approach has been well established and management of these patients requires systematic review of the problems affecting these patients. It appears that strict indication of the surgical intervention with well-documented physical symptoms with laboratory findings provides best guidance for selecting surgical candidates. A meticulous surgical technique, regardless of the method selected to treat these patients, also helps in achieving the best clinical outcomes. It is important to include cervical thymectomy in the surgical plans given high rates of supernumerary of parathyroid gland in patients with renal failure. Finally, patients are best served by surgeons that have gained sufficient surgical experience and clinical expertise in managing these complex patients.

REFERENCES


