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Review

Challenges and controversies in the surgical management of uremic hyperparathyroidism: A systematic review

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ABSTRACT

Background: Prevalence of uremic hyperparathyroidism (uHPT), secondary and tertiary, continues to rise. Historically, surgery was the only durable treatment for these conditions, but with the development of pharmacologic options, the treatment landscape has shifted predominantly towards medical management. Presently, there is a paucity of clear guidelines for surgical indications in the treatment of uHPT. In this review, we will discuss the risks and benefits associated with surgical management of uHPT and will evaluate recent evidence and controversies surrounding indications for parathyroidectomy (PTX) in uHPT.

Data sources: A systematic review of the literature was performed, in accordance with PRISMA guidelines, resulting in the evaluation of 69 articles.

Conclusions: Significant controversy still exists regarding indications and timing of surgical management of uHPT. Although the benefits of PTX in the uHPT patient population have been established, there is a significant need for well-designed randomized clinical trials to further clarify existing guidelines and optimize treatment approaches.

Introduction

As chronic diseases such as diabetes and hypertension become increasingly prevalent, the overall incidence of chronic kidney disease (CKD) in the United States continues to rise, as well. Due to the hormonal axis that exists between the parathyroid glands and kidneys, patients with advancing CKD are more likely to develop the parathyroid disease. Therefore, the incidence of uremic hyperparathyroidism (uHPT), including both secondary (SHPT) and tertiary hyperparathyroidism (THPT) of renal origin, has also been trending upwards.[1,2] The incidence of CKD in the United States is estimated to be 14%.[3] Based on a model described by Hoerger et al. in 2015, the residual lifetime incidence of CKD in Americans aged 30–49 is projected to be 54%.[4] Over 90% of patients on dialysis for end-stage renal disease develop SHPT, and 30% of patients go on to develop THPT following renal transplant.[5,6]

We performed a systematic review of the literature to generate a comprehensive summary of evidence and guidelines regarding surgical management of uHPT. Given the limited scope of published guidelines, the specifics of surgical management remain at the discretion of the individual surgeon. Advances in medical options for management of uHPT have highlighted the need for clinicians to weigh factors such as cost and outcomes when creating a treatment plan. Additionally, the investigation is ongoing regarding the optimal peri- and intra-operative management of uHPT. With this in mind, we focused on literature published in the last decade, highlighting evolving and ongoing controversies in the field, as well as available evidence regarding management. We sought to address the following questions:

1. In adult patients with uHPT, how do survival, biochemical, and cost outcomes compare between patients managed surgically and patients managed medically?
2. What are the available consensus guidelines regarding the surgical management of uHPT in adult patients, and how has recent evidence shaped these guidelines?
3. What are the benefits and complications associated with parathyroidectomy (PTX) performed for uHPT in adult patients?
4. In adult patients with uHPT undergoing PTX, what are important pre-, peri-, and postoperative considerations, and is there evidence that particular surgical approaches yield superior biochemical cure rates or reduced complication rates?

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Methods

Literature search & data source

A systematic review was performed in accordance with the preferred reporting items for systematic review and meta-analysis protocols (PRISMA) guidelines.[7] A comprehensive search of PubMed for studies published before February 1, 2018, was performed using the following electronic search strategies: 1) "surgical management"[tiab] OR "management"[tiab]) AND ("Hyperparathyroidism, Secondary"[Mesh] OR "secondary hyperparathyroidism"[tiab] OR "tertiary hyperparathyroidism"[tiab]) AND English[lang] and 2) "surgical indications"[tiab] OR "indications"[tiab]) AND ("Hyperparathyroidism, Secondary"[Mesh] OR "secondary hyperparathyroidism"[tiab] OR "tertiary hyperparathyroidism"[tiab]) AND English[lang]. After consulting with our institution's research librarian, we elected to use more general search terms, for example, "surgical management" instead of "parathyroidectomy" in order to ensure a more comprehensive search return. Upon receipt of the search results, each contributing author reviewed titles, abstracts, and manuscripts to determine relevance. Notably, a select number of papers were cited in our manuscript outside of our original literature search based on specific reviewer suggestions. These studies are identified in Table 1.

Eligibility criteria

All articles describing management, both surgical and medical, of uHPT in the adult population were included. We excluded articles published more than 10 years ago, excepting older articles deemed to be of historical significance warranting inclusion. Papers included from greater than 10 years ago were included if they provided vital background and framing for our discussion by detailing the basics of pathophysiology and mortality risk. These topics have not been addressed with novelty in more recent literature. We also excluded articles relating to pediatrics and articles written in languages other than English. Both review articles and primary literature (RCTs, cohort studies, case reports, physician surveys, cost analyses) were included. Review articles were primarily utilized for information on basic pathophysiology, routine care practices, and treatment recommendations, given the dearth of standardized guidelines available.

Data collection

An organizational tool was generated using Microsoft Excel in order to categorize articles by subject and relevance. Each author had access to, and editing permissions for, this tool and contributed to the discussion of each articles' relevance but the final decision regarding inclusion and exclusion rested with the senior author. The use of review articles presented a dilemma regarding potential replication of sources and data. The first author systematically analyzed each review article citation within our article and ensured that subsequent citations for the same statement were not also included in the review paper.

Data items & grading evidence

We sought information on biochemical cure rates, overall survival, and total cost of treatment for adults with medically and surgically managed uHPT. We also queried data regarding cardiovascular-specific morbidity and mortality as well as evidence regarding outcomes including bone mineral metabolism, healthcare quality of life, and allograft function. We also report on descriptive studies which characterize the relative rates of different treatments for uHPT being performed. Individual study quality was reported based on Oxford Centre for Evidence-based Medicine-Level of Evidence Guidelines.[8] Strength of recommendations were scored according to Guyatt et al.[9]

Risk of bias

We acknowledge that bias exists at both the individual study and review levels. Each individual study reviewed contains its own inherent limitations and set of biases regarding outcomes and conclusions that have the potential to bias the overall review paper. Thus, each individual study was assessed for bias before inclusion in our review. Additionally, we acknowledge that review-level limitations may have been introduced by our broad topic and the potential for an incomplete literature review. Conversely, a large number of articles included and the wide range of institutions from which they originated may impart a temporizing effect on individual bias.

Results

Study selection

A systematic review of the literature was conducted in accordance with PRISMA guidelines, resulting in the identification of a total of 903 titles (Fig. 1). Sixty-nine articles were found to be appropriate for inclusion, including 7 systematic reviews, 8 general reviews, 27 retrospective cohort studies, 13 prospective cohort studies, 5 randomized controlled trials, and 9 miscellaneous articles.

Secondary hyperparathyroidism

Pathophysiology

CKD is well-established in the literature as the leading cause of SHPT.[6,10] In the setting of CKD, SHPT occurs as a consequence of decreased renal phosphate clearance and impaired vitamin D synthesis, resulting in hypocalcemia. Hypocalcemia leads to chronic stimulation and subsequent hyperplasia of the parathyroid glands, resulting in persistently elevated circulating levels of parathyroid hormone (PTH). These chronically elevated PTH levels drive additional morbidity, including mixed bony lesions, pathologic fractures, bone pain, weakness, pruritis, and calcific uremic arteriolopathy, formerly calciphylaxis.[5,6,10] There is also an increased mortality risk, thought to be primarily due to calcific vascular pathology.[10,11] SHPT, arising most commonly due to mineral dysregulation complications of CKD, presents an additional morbidity and mortality risk to patients.

Considering medical versus surgical management

Medical management has been increasingly utilized in the treatment of uHPT (Table 2). Historically, medical regimens have employed phosphate binders to help control hyperphosphatemia, and vitamin D supplementation to increase gastrointestinal and renal calcium retention, thus normalizing hypocalcemia.[5] More recently, cinacalcet, a calcimimetic agent, has been incorporated into the medical management of SHPT. In a combined analysis of four randomized clinical trials, Cunningham et al. demonstrated that cinacalcet use compared to placebo, when added to a regimen of vitamin D and phosphate binders, reduced the risk for cardiovascular morbidity and pathologic fracture, though there was no associated reduction in mortality.[12] The introduction of calcimimetics has been shown to reduce the number of parathyroidectomies performed for SHPT in the United States, Germany, and Japan, thus shifting the landscape from surgical to

Table 1
Reviewed literature search results by category.

REVIEW OF DISEASE					
AUTHORS	JOURNAL	YEAR	STUDY DESIGN	PRIMARY OUTCOME	LEVEL OF EVIDENCE*
Tomasello S.	*Diabetes*	2008	Review, Unspecified	N/A	5
Dharmarajan SH, et al.	*Am.J.Prev.Med*	2017	Retrospective Review	N/A	2C
Ketteler M, et al.	*Kidney Int.*	2017	Guideline Update	N/A	5
Coates T, et al.	*Am.J.KidneyDis.*	1998	Case Series	Mortality	4
Stevens LA, et al.	*J.Am.Soc.Nephrol.*	2004	Prospective Cohort	Mortality	2B
Tentori F, et al.	*Am.J.KidneyDis.*	2008	Prospective Cohort	Mortality	2B
Block GA, et al.	*J.Am.Soc.Nephrol.*	2004	Retrospective Cohort	Mortality	2B
Messa P, et al.	*Int.J.Neprol.*	2010	Editorial comment	N/A	5
Gioviale MC, et al.	*Ann.Transplant.*	2012	Review, Unspecified	N/A	5
MEDICAL MANAGEMENT ONLY					
AUTHORS	**JOURNAL**	**YEAR**	**STUDY DESIGN**	**PRIMARY OUTCOME**	**LEVEL OF EVIDENCE***
Cohen EP, et al.	*Nephron*	2001	Retrospective Epidemiology Review	Rate of PTX	2C
Cunningham J, et al.	*Kidney.Int.*	2005	RCT	Morbidity	1B
Evenepoel P, et al.	*Am.J.Transplant*	2014	RCT	Biochemical Cure	1B
Ketteler M, et al.	*Nephrol.Dial.Transplant.*	2012	RCT	Biochemical Cure	1B
SURGICAL MANAGEMENT ONLY					
AUTHORS	**JOURNAL**	**YEAR**	**STUDY DESIGN**	**PRIMARY OUTCOME**	**LEVEL OF EVIDENCE***
Pitt SC, et al.	*Surg.Clin.North.Am.*	2009	Review, Unspecified	N/A	5
Triponez F, et al.	*Ann.Surg.*	2008	Systematic Review	N/A	2A
Li S, et al.	*Am.J.Kidney.Dis*	2011	Retrospective Cohort	Rate of PTX	2C
Tominaga Y, et al.	*Ther.Apher.Dial.*	2016	Retrospective Cohort	Rate of PTX	2C
Ivarsson KM, et al.	*Nephrol.Dial.Transplant*	2015	Nested Index Referent Study	Mortality	2C
Kestenbaum B, et al.	*Kidney.Int.*	2004	Prospective Cohort	Mortality	2B
Chen L, et al.	*Ren.Fail*	2016	Systematic Review	Mortality	2A
Messa, P	*Nephrol.Dial.Transplant*	2015	Review, Unspecified	N/A	5
Chen J, et al.	*Nephrology*	2017	Systematic Review	Post-Op Recurrence	2A
Callender GC, et al.	*Surgery*	2017	Retrospective Cohort	Graft Failure	2C
Rothmund M, et al.	*World.J.Surg.*	1991	RCT	Biochemical Cure	1B
Girotto JA, et al.	*Surgery*	2001	Retrospective Cohort	Calciphylaxis Morbidity	2C
Tang JA, et al.	*Am.J.Otolaryngol.*	2017	Systematic Review	N/A	2A
Milas M. & Weber CJ.	*Surgery*	2004	Prospective Cohort	PTX Outcomes/Morbidity	2C
Karipineni F, et al.	*Surgery*	2018	Retrospective Cohort	Gland Localization	2C
Conzo G, et al.	*J.Endocrinol.Invest.*	2012	Prospective Cohort	Biochemical Cure	2C
Anderson K, et al.	*Am.J.Surg.*	2017	Retrospective Cohort	PTX Outcomes/Morbidity	2C
Kievit AJ, et al.	*World.J.Surg.*	2010	Retrospective Cohort	PTX Outcomes/Morbidity	2C
Riss P, et al.	*Langenbecks.Arch.Surg.*	2013	Physician Survey	N/A	5
Triponez F, et al.	*Surgery*	2006	Retrospective Cohort	Post-Op Recurrence	2B
Nichol PF, et al.	*Ann.Surg.*	2002	Retrospective Cohort	PTX Outcomes/Morbidity	2C
Puccini M, et al.	*Gland.Surg.*	2017	Retrospective Cohort	PTX Outcomes/Morbidity	2C
Zou Q, et al.	*Chin.Med.J.*	2007	Prospective Cohort	PTX Outcomes/Morbidity	2C
Ockert S, et al.	*Langenbecks.Arch.Surg.*	2002	Retrospective Cohort	Biochemical Cure	2C
Li C, et al.	*Ren.Fail*	2017	Systematic Review	Post-Op Recurrence	2B
Puccini M, et al.	*Biomed.Pharmacother.*	2010	Prospective Cohort	Biochemical Cure	2C
Lorenz K, et al.	*World.J.Surg.*	2006	Review, Unspecified	N/A	5
Boltz MM, et al.	*Ann.Surg.Oncol.*	2015	Retrospective Cohort	Biochemical Cure	2B
El-Husseini A, et al.	*Nephron*	2018	Prospective Cohort	Biochemical Cure	2B
Hiramitsu T, et al.	*Medicine*	2015	Retrospective Cohort	Biochemical Cure	2C
Joliat GR, et al.	*Medicine*	2017	Prospective Cohort	PTX Morbidity	2B
Oltmann SC, et al.	*Ann.Surg.Oncol.*	2016	Prospective Cohort	PTX Morbidity	2B
Christakis IA, et al.	*Surgery*	2016	Prospective Cohort	PTX Morbidity	2B
Oltmann SC, et al.	*J.Surg.Res.*	2015	Retrospective Cohort	Biochemical Cure	2C
Ho LY, et al.	*BMC Nephrol.*	2017	Retrospective Cohort	PTX Morbidity	2C
Brasier AR. & Nussbaum SR.	*Am.J.Med.*	1988	Retrospective Cohort	PTX Morbidity	2C
Goldfarb M, et al.	*World.J.Surg.*	2012	Prospective Cohort	PTX Morbidity	2C
Miles AM, et al.	*J.Am.Soc.Nephrol.*	1997	Case Report	N/A	5
Ishani A, et al.	*Clin.J.Am.Soc.Nephrol.*	2015	Retrospective Cohort	PTX Outcomes/Morbidity	2C
Chou FF, et al.	*Transplantation*	2008	Prospective Cohort	PTX Outcomes/Morbidity	2B
Littbarski SA, et al.	*Surgery*	2018	Prospective Cohort	Allograft Function	2B
Jeon HJ, et al.	*Transpl.Int.*	2012	Retrospective Cohort	Allograft Function	2C
MEDICAL & SURGICAL MANAGEMENT					
AUTHORS	**JOURNAL**	**YEAR**	**STUDY DESIGN**	**PRIMARY OUTCOME**	**LEVEL OF EVIDENCE***
Shindo M, et al.	*Jour.Am.Coll.Surg.*	2016	Review, Unspecified	N/A	5
Tominaga Y, et al.	*World.J.Surg.*	2009	Systematic Review	N/A	2A
Schlosser K, et al.	*Scand.J.Surg.*	2004	Review, Unspecified	N/A	5
Schneider R, et al.	*Surgery*	2010	Cost Analysis	N/A	2B

(*continued on next page*)

Table 1 (*continued*)

REVIEW OF DISEASE					
AUTHORS	JOURNAL	YEAR	STUDY DESIGN	PRIMARY OUTCOME	LEVEL OF EVIDENCE*
Narayan R, et al.	*Am.J.Kidney.Dis.*	2007	Cost Analysis	N/A	2B
Tominaga Y, et al.	*Ther.Apher.Dial.*	2008	Review, Unspecified	N/A	5
Dulfer RR, et al.	*Br.J.Surg.*	2017	Systematic Review	N/A	2A
Cruzado JM, et al.	*J.Am.Soc.Nephrol.*	2016	RCT	Biochemical Cure	1B
Ghani A. & Baxter P.	*Otolaryngol.Head.Neck.Surg.*	2012	Retrospective Cohort	PTX Outcomes/Morbidity	2C
SURGICAL INDICATIONS					
AUTHORS	**JOURNAL**	**YEAR**	**STUDY DESIGN**	**PRIMARY OUTCOME**	**LEVEL OF EVIDENCE***
Dewberry LC, et al.	*Surgery*	2014	Retrospective Cohort	Biochemical Cure	2C
Tominaga Y, et al.	*Ther.Apher.Dial.*	2005	Review, Unspecified	N/A	5
Araujo MJCLN, et al.	*Surgery*	2018	Prospective Cohort	Graft Failure	2C
Cheng SP, et al.	*Surgery*	2014	Prospective Cohort	Quality of Life	2B
Chou FF, et al.	*Surgery*	2008	Prospective Cohort	Cognitive Function	2B

PTX: Parathyroidectomy.
RTC: Randomized Control Trial.
*Level of Evidence according to the Oxford Centre for Evidence-Based Medicine, Levels of Evidence; March 2009.

predominantly medical management of uHPT.[12–15]

The relative novelty of calcimimetics, widely available since 2004 and the varying data regarding their effectiveness leaves the benefits of surgery over medical management in patients with SHPT as a subject of debate. There is evidence that long-term survival outcomes are more favorable for patients managed surgically.[16–18] In a large retrospective cohort study using the Swedish Renal Registry, Ivarsson et al. demonstrated a survival benefit of 20% associated with PTX for SHPT compared to patients maintained on dialysis and medical therapy.[16] However, it is worth noting that when the authors stratified the patients according to treatment year, and those treated after the widespread introduction of cinacalcet did not see a significant survival benefit associated with PTX.[16] It is unclear if this is due to decreased statistical power, by person-years, or due to superior outcome associated with cinacalcet use, regardless, it leaves clinicians with a clinical dilemma and knowledge gap about the true benefits of either treatment modality.[16,19] Chen et al. published a meta-analysis in 2016 comparing the long-term survival outcomes between patients treated surgically or with cinacalcet.[18] Compared to medical therapy, patients receiving PTX saw a 37% reduction in cardiovascular mortality and a 28% reduction in all-cause mortality.[18]

Unlike Ivarsson, Chen et al. demonstrated that the mortality benefit associated with PTX persisted following the widespread introduction of cinacalcet in 2004 ($z = 3.63$, $p < 0.001$).[18] Though the overall sample size is considerable, this meta-analysis is somewhat limited by the inclusion of smaller studies ($n < 200$) and the fact that it exclusively pooled from cohort studies. Nevertheless, this study provides us with important support for the use PTX in SHPT. Conversely, a recent retrospective cohort study reported that patients who received a PTX for SHPT were at an increased rate of myocardial infarction and arrhythmia-associated hospitalizations

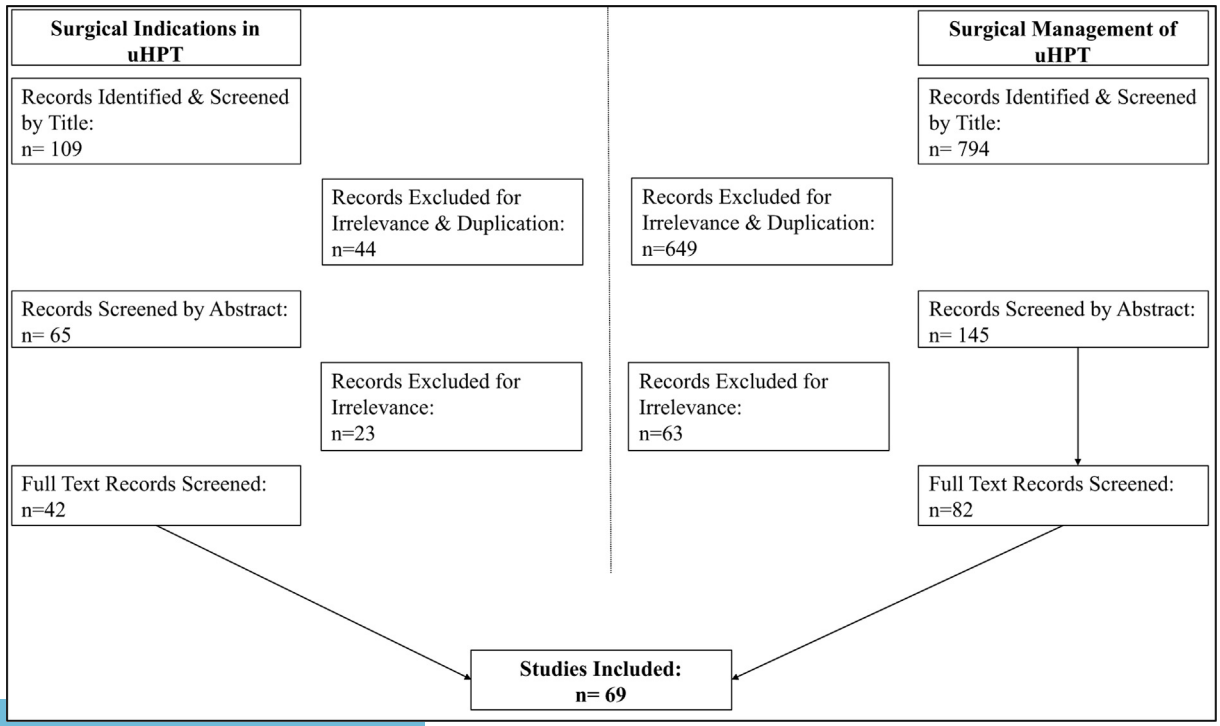

Fig. 1. Literature search flow diagram.

Table 2
Medications commonly used in uremic hyperparathyroidism.

Medication	Mechanism
Cinacalcet	Calcimimetic stimulates CaSR to reduce endogenous PTH production
Paricalcitol	Analog of 1,25-dihydroxyergocalciferol (activated vitamin D). Reduced endogenous PTH production.
Phosphate Binders	Bind and sequester phosphate in the GI tract, preventing hyperphosphatemia in CKD.

over a one-year period compared to patients who were maintained on dialysis.[20] Some of this discrepancy could be due to variation in follow-up times, as well as differing measures of cardiovascular morbidity and mortality. These studies are limited by selection bias because patients selected for the medical management cohort generally had greater comorbidity burdens. The inconsistency between Ivarsson's and Chen's findings on mortality benefit in the cinacalcet era highlights the lack of consensus on management approaches for uHPT that clinicians face routinely. Regardless, large randomized controlled trials are needed to elucidate the cardiovascular and all-cause mortality risk to benefit balance associated with PTX in uHPT.

PTX also provides several other advantages to patients with SHPT. For instance, improved bone metabolism has been associated with PTX. Studies have shown that following PTX, both trabecular bone mineral density and fracture risk are improved in patients with a history of uHPT.[21] Notably, this improvement in bone mineral density occurs even in the absence of renal transplantation, highlighting that patients who may not be candidates for renal transplantation may still derive significant benefit from surgical management with PTX.[21] PTX has also been shown to result in enhanced wound healing, improved pain scores, and greatly decreased mortality in patients with calcific uremic arteriolopathy.[22] Several studies have also shown a quality of life benefit associated with PTX. Cheng et al. used the SF-36 questionnaire to assess emotional and mental health as well as functional status. The authors found that at one year following PTX, SF-36 scores increased significantly, especially in domains such as emotional well-being and vitality.[23] There is also evidence that PTX improves neurocognitive function in patients with SHPT.[24] Chou et al. demonstrated that Mini Mental Status Exam scores increased and clinical dementia rating scores at 16 weeks post-op and were accompanied by a reduction in serum calcium, PTH, and phosphorus.[24] Thus, it is important to consider the potential benefits to patient functional and mental status when considering PTX for UHPT.

Finally, cost considerations support the use of medical management of SHPT primarily as a temporizing method until surgical intervention can be performed. A cost analysis performed by Schneider et al., in 2010 demonstrated that the cost of cinacalcet therapy exceeded the cost of surgical and post-surgical care within nine months of treatment initiation.[14] More specifically, the average annual cost of cinacalcet was 5828.40 euro while the total cost of PTX plus post-operative care cost an average of 4685.40 euro.[14] Narayan et al. similarly found that PTX became more cost-effective than cinacalcet after only seven months of medical therapy.[25] Collectively, these studies provide a glimpse into cost-driven management options and their potential impact on moderating the cost burden on our health care system.

Kidney Disease Improving Global Outcomes (KDIGO) guidelines and evolving indications for parathyroidectomy

2009 KDIGO guidelines. 2009 KDIGO guidelines state that PTX is indicated in patients with CKD stages 3a-5D who have severe biochemical or clinical SHPT refractory to optimal medical management (Recommendation 4.2.5; Level 2B).[26] Given this is the only specific KDIGO guideline available regarding surgical management, several reviews have attempted to compile their own recommendations for when surgery may be indicated.

Commonly clinical indications include refractory pruritis, weakness, and bone pain, as well as intractable side effects of cinacalcet, such as gastrointestinal distress, that may alter adherence.[6,10] Bone disease has also been proposed as an indication for PTX.[27] Additionally, clinically apparent calcific uremic arteriolopathy, formerly calciphylaxis, is a rare but dangerous complication of SHPT and should be considered an absolute indication for PTX.[22] Finally, biochemical SHPT may persist despite resolution of symptoms and the resulting asymptomatic elevations in serum PTH, phosphorus, and calcium have been associated with increased risk of death.[11] Due to this increased risk, refractory asymptomatic biochemical SHPT has also been cited as a reasonable surgical indication for PTX.[10,28–30]

2017 KDIGO guideline updates. The KDIGO 2017 guideline update reflects a changing landscape regarding the surgical management of SHPT.[26] The 2017 KDIGO guideline updates do not set specific goals for serum calcium, phosphate, and PTH levels in patients with CKD, but rather focus on biochemical trends.[26] It is recommended that significant changes in PTH be monitored over time instead of relying on a single measurement, however, when intact PTH levels persist above nine times the upper limit of normal, a change in therapy, which may include PTX, is recommended (Recommendation 4.1.1; Not Graded and Recommendation 4.2.3; Level 2C evidence).[26] It is unclear whether these PTH levels must be obtained off medical therapy or accepted with parallel cinacalcet administration. Further, while earlier guidelines recommended rigid maintenance of normal phosphate levels, it is presently recommended that treatment should only be altered based on hyperphosphatemia in overt, refractory cases (Recommendation 4.1.5; Not Graded).[31] Likewise, the 2017 guidelines state that hypercalcemia should be avoided in adults with CKD G3a-G5D, but no longer stipulates that normocalcemia should be maintained (4.1.3; Level 2C).[26] The collective relaxation of these regulations may potentially spare patients unnecessary treatment and associated morbidity, but also furthers controversy over the optimal timing of PTX.

Tertiary hyperparathyroidism

Pathophysiology

THPT is classified as persistently high PTH levels following renal transplant and is characterized by hypercalcemia, hypophosphatemia, decreased bone density, and increased risk for pathologic fracture.[6] The mechanism of disease is thought to result from parathyroid hyperplasia that fails to involute following renal transplant, typically as a consequence of prolonged secondary disease.[6,32] Most cases of THPT regress within several months of renal allograft, decreasing the need for additional intervention.[33] Preoperative predictors for the development of THPT include markedly elevated serum calcium or PTH levels, prolonged duration of dialysis, and use of calcimimetics.[32,34]

Considering medical versus surgical management

While controversy exists regarding medical versus surgical management in SHPT, it is generally accepted that surgery is the only definitive treatment for THPT.[5,6,35] While cinacalcet has been shown to induce a very high biochemical cure rate in THPT, it remains relegated to off-label use and thus incurs a very high cost to the patient.[33,36,37]

In contrast to PTX for SHPT, the number of surgeries being performed on patients with tertiary disease seemed not to be impacted by the introduction of cinacalcet.[13,15] The only randomized clinical trial on the subject, published by Cruzado et al., demonstrated that PTX was superior to cinacalcet in restoring normocalcemia in patients with THPT.[38] This study did not demonstrate any difference in fracture risk, mortality, or graft function, though these findings must be considered within the context of small sample size and short study duration.[38] While PTX is associated with a more favorable biochemical and morbidity profile, a large retrospective cohort study by Ivarsson et al., showed no mortality benefit associated with PTX in patients with THPT following renal transplant.[16] Thus, while surgery remains the mainstay of treatment for the relatively rare complication of THPT, higher-powered randomized control trials are needed to determine if there is a definitive survival benefit associated with PTX for THPT as compared to optimal medical management.

There is also growing evidence that PTX has beneficial effects on kidney allograft function. Persistent hypercalcemia following transplant can result in nephrocalcinosis, leading to papillary or urinary tract damage, and can cause microscopic or macroscopic renal lesions.[39] Furthermore, some investigators have posited a link between THPT and a compounded risk for post-transplant acute tubular necrosis.[40] In a recently published prospective cohort study performed by Littbarski et al., the authors found that post-transplant PTX was associated with a higher risk of graft compromise (KDIGO Stage ≥ 4) one year after transplant when compared to pre-transplant PTX.[41] Similarly, other retrospective cohort studies have suggested that pre-transplant PTX lowers the risk for renal allograft functional deterioration.[42–44] Interestingly, Littbarski et al. found that graft function, measured by glomerular filtration rate (GFR), declined without subsequent recovery to pre-PTX levels if the surgery was performed within one year following receipt of allograft. Graft function did not significantly decline in patients who underwent PTX more than one year after transplant, leading authors to recommend definitive surgery be performed either prior to transplant or well after transplant.[41] In contrast, Araujo and colleagues found that a PTH level of 150 pg/ml was a strong predictor of persistent HPT at one year, and thus advocated for early PTX following transplant.[42] Collectively, these data detail the potential benefit to graft function associated with PTX, and highlight the ongoing controversy surrounding the timing of PTX relative to transplant. Randomized clinical trials are needed to verify these findings in order for consensus to be reached and strong evidence-based recommendations to be made.

Evolving indications for parathyroidectomy

THPT is a relatively rare condition, occurring in only 1–3% of patients with ESRD, but may occur in up to 30% of all renal allograft recipients.[6,45] As discussed above, there is a general consensus that surgical management is superior to medical management in THPT. There are currently no evidence-based indications for PTX in THPT, but surgery is generally delayed for at least one year after transplant.[33] A systematic review performed by Tang et al., in 2017 provides an excellent summary of the existing data regarding surgical indications for THPT. Out of the 30 studies surveyed, the most commonly cited indication for surgery in THPT was symptomatic hypercalcemia.[45] Other clinical indications for PTX in THPT include nephrocalcinosis, severe pruritis, and low bone mineral density.[33] Therefore, indications for PTX in THPT are fairly broad and generally relate to the symptoms of hypercalcemia. The role of PTH level as an indication for surgery in THPT remains an area for further exploration.[45]

Surgical management of UHPT

Preoperative risk stratification

Patients with ESRD and UHPT on hemodialysis (HD) or peritoneal dialysis (PD) require multidisciplinary preoperative risk stratification in order to reduce perioperative surgical and anesthetic complications that may arise in the background of their co-morbidities. Based on varying disease progression and differing co-morbidity profiles, it is impractical to pursue standardized, universal cardiac risk evaluation. Instead, it is important to tailor the preoperative cardiac risk assessment to stratify each patient.[46,47] Due to uremic platelet dysfunction experienced in this population, it is important to assess the coagulation status of each uHPT surgical candidate with prothrombin time (PT), activated partial thromboplastin time (aPTT), the international normalized ratio (INR), and a platelet count.[46] Preoperative desmopressin administration may be helpful in these patients and has been shown to improve platelet dysfunction.[48] Patients may often be on anticoagulation regimens that require careful assessment and discussion with clinicians involved in patient's care prior to altering their prescribed regimens preoperatively. Hemodialysis and peritoneal dialysis should be performed one day preceding surgery with the goal of bringing the patient as close to their baseline “dry” weight as possible. Longitudinal planning of pre-, peri-, and post-operative volume status should occur preoperatively between the surgical and nephrology teams.[46,47]

Preoperative gland localization

Preoperative gland localization remains a source of ongoing controversy. Cervical ultrasonography (US) is the most commonly utilized preoperative imaging modality in patients with UHPT, allowing for both assessment for hyperplastic parathyroid glands and evaluation of the thyroid gland for any abnormalities that would necessitate surgical intervention at the time of PTX.[6] 99mTc sestamibi scintigraphy is commonly employed in conjunction with US and is primarily used to identify ectopic, mediastinal parathyroid glands otherwise not detected by US.[47] Preoperative sestamibi scanning has the potential to confer benefit in two ways. First, accurate preoperative gland localization facilitates rapid intraoperative identification and leads to decreased operative times which benefit the surgically fragile uremic patient population. Second, early identification of ectopic glands facilitates comprehensive intraoperative excision and decreases the risk of recurrence due to retained ectopic tissue. Further, a study by Karipineni et al. further supported the importance of sestamibi scanning by demonstrating that the sensitivity of sestamibi for ectopic glands was 29%, while the sensitivity of US for ectopic glands was only 7%.[49]

Despite theoretical advantages, much of the literature on the topic suggests that accurate preoperative imaging with both US and sestamibi is very limited. In fact, a study by Milas and Weber demonstrated that preoperative imaging identified only 38% of patients that later were found to have ectopic mediastinal parathyroid glands intraoperatively.[50] In a patient population with a high risk of recurrence in the setting of unidentified parathyroid tissue is left in place, many surgeons argue strongly for preoperative imaging localization. However, some also argue against preoperative localization imaging on the grounds that the results are unlikely to change their surgical management and that the

standard of care remains a bilateral neck exploration.[6]

Finally, preoperative medical optimization with varying regimens of calcitriol and vitamin D supplementation appear in the literature, and it is an important consideration to be further explored. The preoperative calcitriol and vitamin D supplementation is thought to primarily ameliorate the postoperative complications of postoperative hypocalcemia and hungry bone syndrome (HBS).[5,47] Further studies are needed to better understand the impact and benefits of these preoperative regimens on long-term postoperative outcomes in patients with uHPT.

Operative approaches

The three main surgical approaches described in the treatment of uHPT include subtotal parathyroidectomy (SPTX), total parathyroidectomy with autotransplantation (TPTX-A), and total parathyroidectomy without autotransplantation (TPTX). SPTX involves removal of most parathyroid tissue while leaving a remnant of one gland *in situ*. TPTX involves removal of all four parathyroid glands and may be accompanied by autotransplantation of a normal gland remnant, usually in the forearm. Historically, bilateral neck exploration with gland cryopreservation was generally offered to all patients, however, a significant cost associated with parathyroid cryopreservation and significantly reduced parathyroid gland viability post-cryopreservation has shifted the practice away from cryopreservation altogether.[6] At present, there is no overwhelming evidence that one surgical approach is superior over another for treatment of uHPT, though small studies have suggested that TPTX yields the lower rates of recurrence.[5,51] A meta-analysis by Chen et al., comprised of 13 studies and 1589 patients with renal failure, demonstrated no significant difference between TPTX-A or SPTX in terms of recurrence of hyperparathyroidism, symptomatic improvement, or need for reoperation.[52] Additionally, odds of readmission, complications, and 30-day mortality were comparable between these two approaches.[53]

SPTX and TPTX-A are the most commonly performed procedures for UHPT.[54] In the case of SPTX, reduction of the enlarged parathyroid gland to the size and weight roughly equivalent to two to three normal parathyroid glands seems to be sufficient to demonstrate adequate reduction of PTH levels leading to high rates of biochemical cure over two years.[5] SPTX does carry the potential benefit of preserving gland vascularity and function in the perioperative period, but there is no durable evidence that this correlated with a lower risk of postoperative hypocalcemia. Recurrence following SPTX will often require a challenging neck re-exploration while TPTX-A allows easier access to re-implanted glands. However, placement of a radiopaque marker, such as a titanium clip or non-absorbable suture, can decrease the difficulty of neck re-exploration, as can preservation of an inferior gland, due to its more anterior location.[6,47]

Compared to other approaches, TPTX (without autotransplantation), though controversial and not commonly utilized in clinical practice by most surgeons, has garnered a lot of interest due to its conceptual drive to minimize the chance for disease persistence in SHPT. Namely, patients who receive TPTX have reported SHPT recurrence rates of 0–4% while patients treated with TPTX-A have recurrence rates ranging from 5-80%.[55,56] Post-TPTX recurrence is likely to be due to various factors, such as incomplete excision of all parathyroid glands, supernumerary ectopic glands and potential small parathyroid embryologic rests that were not identified intraoperatively. A recent meta-analysis performed by Li et al., which included 10 cohort studies and a single RCT, also showed a decreased risk of reoperation and disease recurrence following TPTX as compared to TPTX-A.[57] Though reoperation carries less morbidity in patients with transplanted parathyroid tissue as compared to patients who receive SPTX, TPTX alone may potentially spare a patient from undergoing even a minor second procedure. While there is a risk for acute post-operative hypocalcemia, this typically develops into mild, supplement-responsive permanent hypoparathyroidism.[58] Others have demonstrated that the risk of these complications is no different than those following SPTX and thus argued that especially when combined with gland cryopreservation, TPTX should be the surgical approach of choice in uHPT.[59]

The addition of transcervical thymectomy, regardless of PTX approach, has been widely endorsed in the treatment of UHPT, and may account for reduced recurrence rates following PTX.[6,54,60] Approximately 32% of uHPT patients have been shown to have ectopic parathyroid glands, most commonly located in the thymus.[5] In a single-center retrospective study published in 2015, Boltz et al. found that 18% specimens obtained from patients who underwent PTX with associated bilateral transcervical thymectomy for uHPT contained supernumerary glands.[60] The chronic parathyroid stimulation found in SHPT and THPT can cause hyperplasia of small supernumerary parathyroid tissue elements in the thymus that could contribute to recurrent disease, if not resected.[5,47] Further, the overall cure rate associated with PTX for uHPT was shown to be higher in patients who had received bilateral prophylactic thymectomy.[60] Therefore, surgical removal of the cervical horns of the thymus is recommended during surgical management of SHPT and THPT.[47]

Intraoperative PTH monitoring

Intraoperative PTH (IOPTH) monitoring is a well-established mechanism for predicting successful PTX in PHPT, however, the IOPTH effectiveness is less clear in SHPT and THPT.[61] This is primarily due to decreased renal clearance of PTH due to pervasive renal failure in patients with SHPT.[5] Therefore, the appropriate degree to which PTH is expected to drop intraoperatively is not well-established and remains a subject of debate. In studies evaluating uHPT patients, a 50–70% intraoperative drop in PTH is most commonly cited as predictive of surgical success.[47,62] However, IOPTH goals in uHPT patients are unclear, with many clinicians opting for acceptable PTH values in low hundreds. IOPTH returning to normal range perioperatively is a common metric used in PHPT but this is a less effective determinant of surgical success in uHPT due to the drastically elevated PTH levels.[47] Therefore, while specific guidelines have not been established, IOPTH monitoring may be helpful in assessing for adequacy of parathyroid gland resection during PTX for uHPT.

Postoperative considerations

Complication rates vary greatly between institutions, but the most common postoperative complications of PTX for UHPT include recurrent laryngeal nerve damage (albeit very low risk), severe hypocalcemia, hematoma, and permanent hypoparathyroidism.[6] Recurrent laryngeal nerve (RLN) injury is an extremely rare complication of PTX.[63] Nerve transection warrants an immediate repair at the time of resection (including possible intraoperative otolaryngology consultation), as well as postoperative referral to otolaryngology. However, most minor nerve injuries typically resolve within six months of operation, and if not resolved, referral to an otolaryngologist or speech therapist will follow.[63] Airway compromise from rapidly developing cervical hematoma can be a fatal complication of both thyroid and parathyroid surgery, if not recognized in a timely fashion. Uremic patients receiving anticoagulation or antiplatelet therapy are at a significantly greater risk of postoperative hematoma in the immediate postoperative period and warrant close, inpatient monitoring.[64] Management of cervical hematoma may include emergent bedside decompression, followed by careful, well-coordinated, and,

if available, video-assisted intubation by anesthesia to secure airway post-decompression.[65,66]

The severe and refractory hypocalcemia following PTX has been defined as the hungry bone syndrome (HBS). HBS was first described as a syndrome in 1948 and has since accumulated a great many variations in its clinical definition.[67] Most commonly, HBS is defined by severe and prolonged hypocalcemia lasting longer than three to four days postoperatively.[67,68] Other studies incorporate hypophosphatemia, the need for IV calcium gluconate, and additional hospital days into the definition of HBS.[69,70] To assess for postoperative hypocalcemia and hypoparathyroidism, serum calcium levels should be monitored frequently at least two days postoperatively, and serum PTH levels should be documented at least one day postoperatively.[47] Management of postoperative hypocalcemia in uremic patients includes a high calcium bath dialysate, aggressive oral calcium repletion, and an oral calcitriol regimen.[5,47] If postoperative hypocalcemia is severe or refractory to maximum oral calcium repletion, then an intravenous calcium drip infusion may be initiated until serum calcium levels are normalized on an oral regimen and are maintained off the drip.[5]

Limitations of surgical management

Notably, surgery is not feasible for all patients with UHPT. PTX may present an undue risk to patients who are unlikely to tolerate anesthesia due to severe co-morbidities, whose parathyroid glands are difficult to access or completely resect, and patients with prior neck manipulation or percutaneous ethanol injections.[35] Collectively, PTX is an option for most patients with medically refractory SHPT or THPT, though patients with many co-morbidities or challenging anatomy should be screened carefully.

Conclusion

As chronic diseases like hypertension and diabetes impact increasing numbers of Americans, the incidence of CKD and uHPT will continue to rise. Nearly 15 years after the introduction of cinacalcet, the balance between medical and surgical management of uHPT continues to shift. Over the past decade, KDIGO guidelines have stated that surgery should be reserved for patients with medically refractory disease, a statement that has been paralleled by a concomitant decline in PTX being performed for renal hyperparathyroidism.[12,13,26] 2017 KDIGO guidelines have highlighted the importance of charting PTH levels over time, suggesting that persistent elevations over nine times the upper limit of normal should be considered an indication for PTX (Level 2C evidence).[26] Several large retrospective cohort studies have demonstrated superior survival and biochemical cure rates, as well as more favorable cost profiles associated with PTX compared to medical management (Level 2C evidence).[14,16,18,25,36] PTX carries additional benefits such as decreased renal allograft failure rate, improved neurocognitive function, and improvement of symptoms (Level 2C Evidence).[23,24,43,44] Further, given the potential benefits associated with early PTX, improved interdisciplinary coordination is needed to refer surgical candidates in an expedited manner.[41] There are no definitive guidelines as to the role of PTX in patients with CKD prior to dialysis and this topic needs to be explored further.

Currently, choice of procedure for PTX is up to the individual surgeon, given the similar cure rates observed between techniques.[52] Further, the optimal gland remnant weight in the case of SPTX remains a subject of debate.[71–73] One must weigh factors such as ease of reoperation, the risk for remnant gland failure, the risk of bleeding, and patient comorbidities during surgical planning. Patients may be offered gland cryopreservation, bilateral prophylactic thymectomy, and intra-operative PTH monitoring, though the efficacy of the latter in uHPT has not yet been firmly established.[5,47]

We acknowledge that limitations exist at both the outcome and review levels. Each individual study reviewed contains its own inherent limitations and set of biases regarding outcomes and conclusions that have the potential to bias the overall review paper. Additionally, though we believe that we performed a thorough literature review, we acknowledge that review-level limitations may have been introduced by our broad topic and the potential for an incomplete literature review.

At present, the guidelines for surgical indications for PTX in uHPT are still under debate. In general, PTX should be offered to patients with medically refractory uHPT, or in cases of severe complications, such as uremic calcific arteriolopathy (Level 2B Evidence). There are various quality-of-life measures that improve following PTX, adding to the cardiovascular and overall survival benefits (Level 2C Evidence). When considering the timing of PTX in uHPT, one must weigh factors such as the feasibility of follow up and benefits to graft function. Recent retrospective cohort studies and meta-analyses have worked to elucidate the challenges and controversies surrounding surgical management of uHPT. However, there is a significant need for future randomized clinical trials aimed at investigating unanswered questions and establishing uniform, streamlined, evidence-based practice guidelines for the surgical treatment of patients with uHPT.

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