PARATHYROID GLAND VOLUME AS ONE OF THE INDICATORS FOR PARATHYROIDECTOMY IN SECONDARY HYPERPARATHYROIDISM

HO KAH YEE

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE SURGERY

SCHOOL OF MEDICAL SCIENCES

UNIVERSITI SAINS MALAYSIA

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SUPERVISORS:

DATO' PADUKA PROFESSOR DR MOHD ZIYADI GHAZALI

MS SITI ZUBAIDAH BINTI SHARIF

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First and foremost I would like to give praise and thanks to the Lord for watching over me as I completed this research project. The amount of pressure was immense as the deadline approached and it was only through His strength that I was able to persevere and complete this project. Starting a research project from scratch required a lot of patience and determination. There were times when I felt despair, an impending sense of doom seemed to cloud my thoughts. And it was at times like these that I found myself turning to the Lord for guidance and to draw strength from His words of wisdom, for it says in the bible, "He gives strength to the weary and increases the power of the weak…But those who wait on the Lord shall renew their strength" (Isaiah 40:28-31). In all ways, the Lord gave me support, and kept me emotionally sane and physically fit to be able to fulfill the requirements of completing this task.

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Last but not least, I would like to express my deepest gratitude to my husband and family members. I first seek forgiveness from all those closest to me for being unable to carry out my duties as a wife and a filial daughter due to the distance between us. I thank you for always understanding the motive behind my actions, and forgiving my absence and misdeeds. There have been many tears shed over the course of this study, and I have shared with you my angst and frustration. Thank you for listening, and thank you for always providing a shoulder to cry on. Thank you for being there to catch me when I fall.

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMNS

ALP	Alkaline phosphatase
CaSR	Calcium sensing receptor
CKD	Chronic kidney disease
iPTH	Intact parathyroid hormone
MBD	Mineral bone disease
NICE	National Institute for Health and Care Excellence
PTH	Parathyroid hormone
sHPT	Secondary hyperparathyroidism
SPTX	Subtotal parathyroidectomy
TPTX	Total parathyroidectomy without autotransplantation
TPTX + AT	Total parathyroidectomy with autotransplantation
VDR	Vitamin D receptor

ISIPADU KELENJAR PARATIROID SEBAGAI SATU PETUNJUK UNTUK PARATIROIDECTOMI BAGI PESAKIT HIPERPARATIROIDISME SEKUNDER

ABSTRAK

Latar Belakang

Hiperparatiroidisme sekunder berlaku akibat kegagalan buah pinggang untuk menyediakan homeostasis kalsium dan fosfat yang mencukupi dalam penyakit buah pinggang kronik. Dalam jangka masa panjang, terdapat gangguan berkaitan metabolisme tulang yang berikutan, yang membawa kepada ketidakupayaan fizikal. Rawatan hiperparatiroidisme sekunder berpusat di sekitar kawalan hiperphosphatemia dan hipocalcemia , dan ini boleh dicapai melalui terapi perubatan atau pembedahan untuk mengeluarkan kelenjar paratiroid. Kajian ini bertujuan untuk menentukan isipadu kelenjar paratiroid berkaitan dengan tahap hiperplasia, dan seterusnya menggunakan isipadu kelenjar paratiroid sebagai penunjuk untuk paratiroidectomi.

Kaedah Kajian

Ini adalah kajian kes yang dijalankan di Hospital Queen Elizabeth II, Kota Kinabalu , Sabah . Ia melibatkan pesakit peringkat akhir penyakit buah pinggang menjalani rawatan dialisis, yang telah menjalani paratiroidectomi untuk hiperparatiroidisme menengah dari 1 Januari 2012 hingga 31 Disember 2017. Kajian ini

merangkumi semua pesakit yang telah menjalani paratiroidectomi dalam tempoh kajian itu, dan tidak termasuk pesakit dengan hiperparatiroidisme utama, pesakit dengan penanda biokimia yang tidak lengkap sebelum pembedahan, dan mereka yang mempunyai dokumentasi hasil histopatologi yang tidak lengkap . Data tersebut kemudiannya dianalisis dan hasil yang dihasilkan menggunakan perisian Perisian Statistik Sosial Sains (SPSS) versi 24.

Keputusan

56 pesakit yang telah menjalani paratiroidectomi untuk hiperparatiroidisme sekunder telah dikaji. Kami mencatatkan keputusan yang kurang baik dengan ultrasonografi untuk mengesan kelenjar paratiroid dalam tetapan kami. Tidak terdapat hubungan yang signifikan antara isipadu sebenar kelenjar paratiroid seperti yang dilihat pada pemeriksaan histopatologi, atau isipadu berdasarkan ultrasonografi dengan tahap hiperplasia kelenjar. Tidak terdapat juga hubungan yang signifikan di antara tahap iPTH sebelum pembedahan dengan saiz kelenjar mahupun tahap hyperplasia kelenjar tersebut.

Kesimpulannya

Isipadu kelenjar paratiroid tidak boleh digunakan sebagai penunjuk tunggal paratiroidectomi. Walaupun ultrasonografi berguna sebagai penilaian yang tidak invasif terhadap tindak balas terhadap terapi perubatan, kami gagal untuk menunjukkan kepentingan isipadu kelenjar dengan tahap hiperplasia, yang menunjukkan tindak balasnya terhadap terapi perubatan. Oleh itu kami mencadangkan bahawa parameter lain seperti tahap iPTH sebelum pembedahan dan gejala gangguan tulang mineral perlu diambil kira sebelum paratiroidectomi.

THESIS TITLE

ABSTRACT

Background

Secondary hyperparathyroidism occurs as a result of the failure of the kidneys to provide adequate calcium and phosphate homeostasis in chronic kidney disease. In the long run, there are other associated disorders of bone metabolism that follows, leading to incapacitating disabilities. Treatment of secondary hyperparathyroidism is centered around the control of hyperphosphatemia and hypocalcemia, and this can be achieved by medical therapy or surgery to remove the parathyroid glands. This study aims to determine the volume of the parathyroid gland in relation to its degree of hyperplasia, and subsequently to use the volume of the parathyroid gland as an indicator for parathyroidectomy.

Methods

This is a case control study conducted in Hospital Queen Elizabeth II, Kota Kinabalu, Sabah. It involves patients with end stage renal disease on dialysis, who have undergone parathyroidectomy for secondary hyperparathyroidism from 1st January 2012 until 31st December 2017. The study includes all patients who have undergone parathyroidectomy in the study period, and excludes patients with primary hyperparathyroidism, patients with incomplete biochemical markers prior to surgery, and those with incomplete documentation of histopathological results. The data is then

analyzed and results generated using Statistical Package for the Social Sciences (SPSS) software version 24 .

Results

56 patients who had undergone parathyroidectomy for secondary hyperparathyroidism were studied. We noted poor results with ultrasonography on detection of parathyroid glands in our setting. There was no significant relationship between the actual volume of the parathyroid gland as seen on histopathological examination, or the volume on ultrasound with the degree of hyperplasia of the gland. There was also no significant relationship between the preoperative iPTH levels an the size of the gland nor the degree of hyperplasia of the gland.

Conclusion

The volume of the parathyroid gland should not be used as the sole indicator of parathyroidectomy. While ultrasound is useful as a non-invasive assessment of the response to medical therapy, we failed to demonstrate the significance of the volume of the gland with the degree of hyperplasia, which reflects on its response to medical therapy. Therefore we suggest that other parameters such as preoperative iPTH levels and symptoms of mineral bone disorders should be taken into consideration prior to parathyroidectomy.

CHAPTER 1

INTRODUCTION

1.1 Brief History

The parathyroid gland is one of the last anatomical discoveries in humans. Sir Richard Owen was the first to describe the parathyroid glands in a rhinoceros. However, it was Ivar Sandstrom who discovered the parathyroid gland in the late 19th century in Uppsala, Sweden. He noted upon dissection of autopsy cases that there was a small organ on both sides of the inferior border of the thyroid gland, which was distinguishably different from the thyroid gland and lymph node. The functional importance of the parathyroid glands were discovered by Eugene Gley, who described the fatal seizures that followed after thyroidectomy, and through a series of experiments, he was able to conclude that it was the removal of the parathyroid glands that contributed to this effect. Giulio Vassale and Francessco Generali further demonstrated tetany after thyroid and parathyroid removal, and later on in the early 20th century, others were able to demonstrate fatal tetany after complete parathyroid removal, which proved that parathyroid tissue was absolutely necessary for survival (Medvei, 1982; Eknoyan, 1995).

1.2 Surgical Anatomy

The parathyroid glands are usually 4 in number, and have different embryological origins. The superior parathyroid glands originate from the fourth branchial pouch, whereas the inferior parathyroid glands originate from the third branchial pouch. During migration of the glands, the superior parathyroids settle at the posterior aspect of the thyroid gland near the cricothyroid junction, while the inferior parathyroids have a more variable descent. Common sites to locate the inferior parathyroid glands are inferior, lateral or posterior to the inferior thyroid pole below the inferior thyroid artery, in the thymus, or even in the anterior mediastinum (Miller, 2003). The blood supply to the parathyroid glands are derived from the inferior thyroid arteries, and to a lesser extent the superior thyroid arteries.

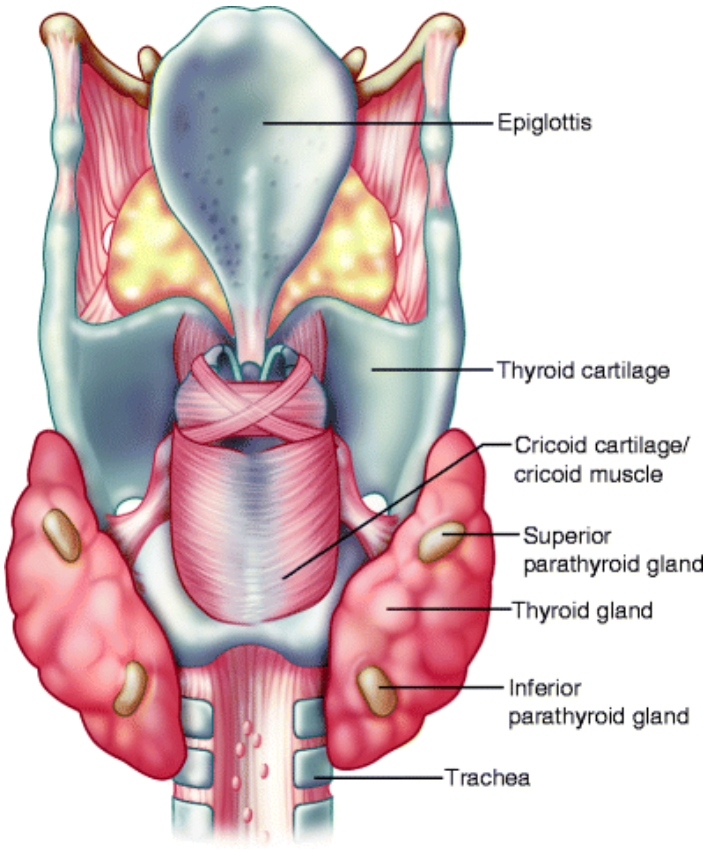


Figure 1: Anatomy of superior and inferior parathyroid glands

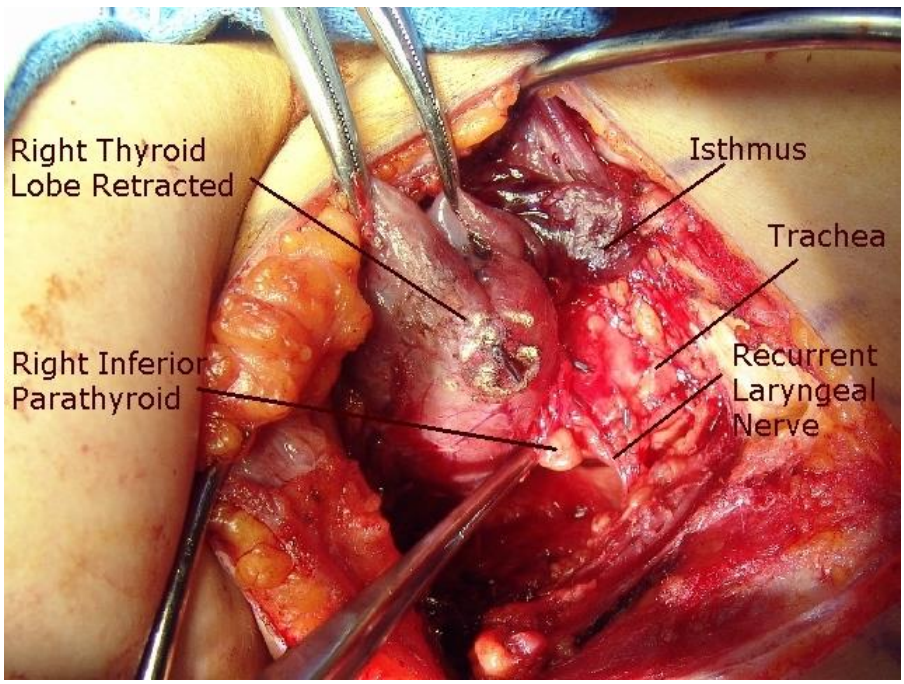


Figure 2: Anatomy of inferior parathyroid gland in relation to recurrent laryngeal nerve (Ghorayeb, 2014)

1.3 Pathophysiology

1.3.1 Pathophysiology of Secondary Hyperparathyroidism

Fuller Albright described parathyroid hyperplasia, and explained that there was a distinction between parathyroid hyperplasia with hyperparathyroidism and compensatory hyperplasia of parathyroid glands (Albright *et al.*, 1934). This formed the basis of the difference between primary, secondary, and tertiary hyperparathyroidism.

Secondary hyperparathyroidism (sHPT) occurs most commonly "secondary" to chronic kidney disease (CKD), and therefore frequently referred to as renal hyperparathyroidism. The pathophysiology lies in the relationship between CKD and parathyroid hyperplasia. The inability of the kidneys to maintain proper calcium and phosphorus homeostasis stimulates glandular hyperplasia. This happens when there is initial failure of the kidneys to excrete phosphate, leading to hyperphosphatemia.

It is believed that hyperphosphatemia is the major factor that causes parathyroid gland hyperplasia in sHPT. There were experimental studies that showed that restriction of phosphate in the diet was associated with no increment in the PTH levels, which may delay the onset of sHPT (Slatopolsky *et al.*, 1971). The series of events that occur in hyperphosphatemia is represented in Figure 3.

The high phosphate levels induce parathyroid hormone (PTH) secretion by:

- direct stimulation of the parathyroid glands
- precipitation with calcium, leading to mild hypocalcemia
- downregulating vitamin D receptors (VDR) on the parathyroid glands, causing vitamin D resistance. This is then seen as a loss of negative feedback on the parathyroid glands, causing the release of high levels of PTH (Saliba and El-Haddad, 2009)

sHPT at late stages progresses to involve disorders of bone as well as soft tissue calcifications, which may prove to be life threatening

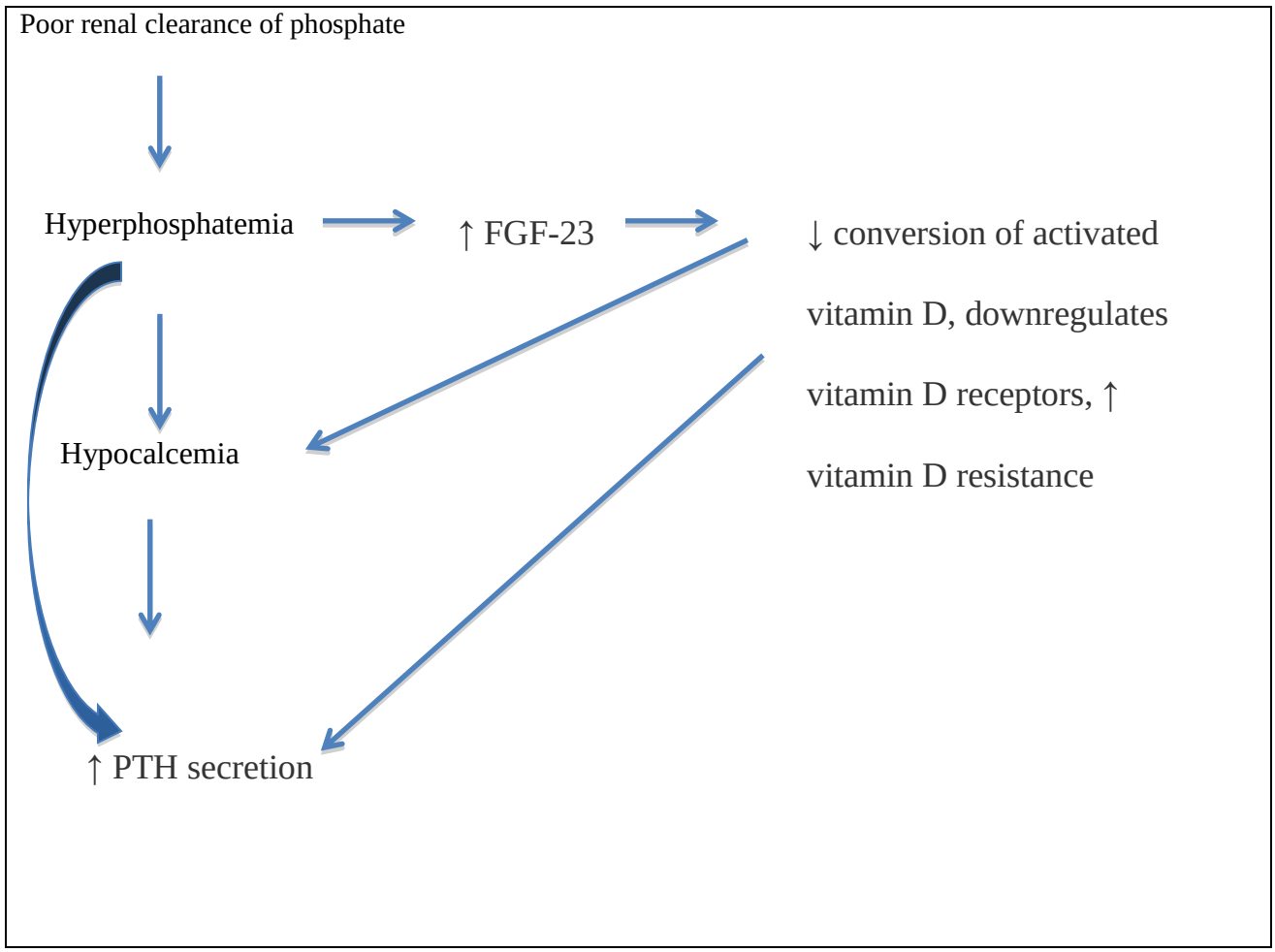
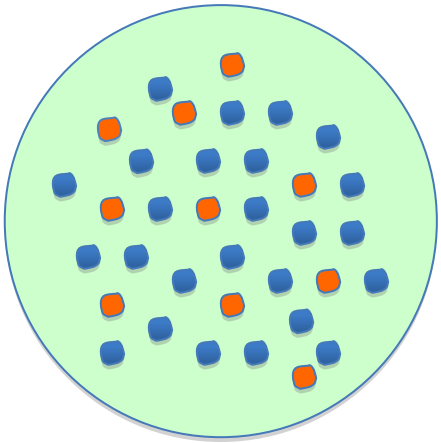


Figure 3: Calcium and phosphorus metabolism in renal failure. PTH – parathyroid hormone, FGF-23 – fibroblasts growth factor 23.

1.3.2 Pathophysiology of Glandular Hyperplasia

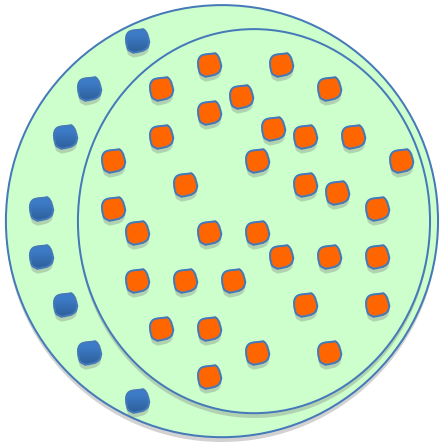
Cellular adaptation is a process that may be physiological or pathological. Hypertrophy and hyperplasia can be seen as a compensatory response to the increased demands and needs of the body. Organs such as the muscle undergo hypertrophy from repeated use, and organs such as the uterus may undergo hyperplastic changes in preparation for pregnancy. The parathyroid gland is not excluded from cellular adaptation, and its growth is stimulated by hypocalcemia and hyperphosphatemia.

As CKD progresses, there is constant stimulation to produce higher amounts of PTH. In order to meet the high demand for production of PTH, the parathyroid glands undergo hyperplasia. However there are variations in the size and morphology of the gland even in the same patient, which differentiates parathyroid hyperplasia from other forms of hyperplasia in other organs (Fukagawa *et al.*, 2006). An illustration of the progression of hyperplasia is pictured in Figure 4. Prolonged stimulation of the parathyroid glands leads to an initial diffuse polyclonal hyperplasia, followed by monoclonal nodular hyperplasia. At the stage of nodular hyperplasia, there is a significant decrease in expression of calcium-sensing receptors (CaSR) and vitamin D receptors (VDR), both of which are key in the regulation of parathyroid hormone production and secretion (Goto *et al.*, 2008). It is postulated that nodular hyperplasia of the parathyroid glands is related to failed medical therapy, and hence, surgery is the treatment of choice for hyperparathyroidism (Tominaga *et al.*, 2007).



Diffuse hyperplasia:

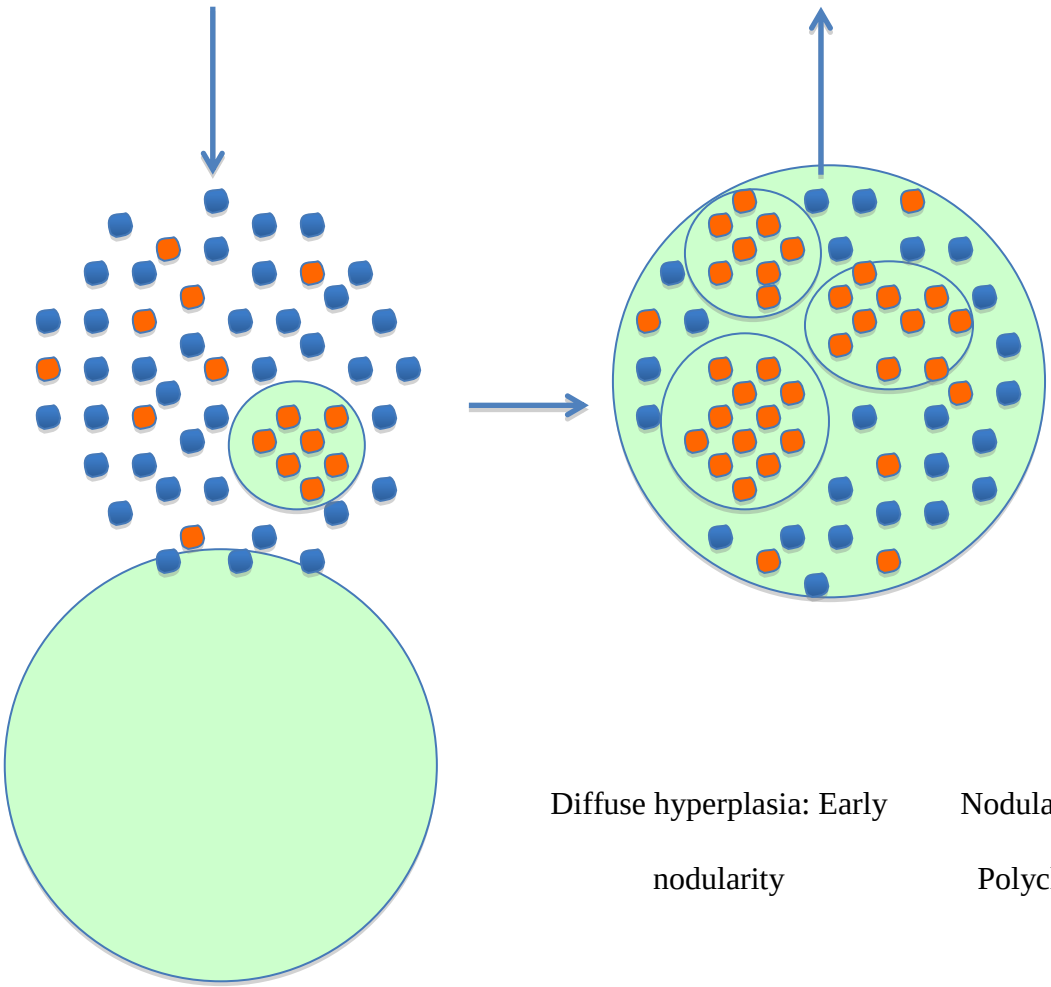
Polyclonal growth



Nodular hyperplasia: Single

nodule with monoclonal

growth



Diffuse hyperplasia: Early

nodularity

Nodular hyperplasia:

Polyclonal growth

Figure 4: Schematic representation of the stages of parathyroid gland hyperplasia in CKD patients based on Tominaga's classification.

1.4 Management of Secondary Hyperparathyroidism

1.4.1 Medical Therapy

Management of sHPT revolves around controlling hyperphosphatemia and maintaining calcium levels at an acceptable range. Previously, surgical indications for parathyroidectomy were based on the evidence of bone disease. The new trends in pharmaceutical drugs have strongly influenced the management of sHPT, and the suppression of parathyroid hormone can be achieved by phosphate binders, vitamin D receptor analogues, and/or calcimimetics. However, when the disease is refractory to medical therapy, surgery is still considered to be the treatment of choice.

In our setting, most patients with CKD receive phosphate binders such as calcium carbonate, and vitamin D receptor analogues such as calcitriol to prevent progression of bone disease. However, access to newer and more effective drugs such as paricalcitol and cinacalcet are limited due to the high costs involved. Calcimimetics such as cinacalcet are superior to calcitriol in its ability to increase the sensitivity of CaSR to extracellular calcium and therefore reducing parathyroid gland stimulation and proliferation.

In experiental studies, cinacalcet is seen to decrease parathyroid gland proliferation with reduction in size, and thus delayed the onset of secondary hyperparathyroidism

(Colloton *et al.*, 2005). Meta analysis and randomized control trials involving cinacalcet and other conventional therapies have confirmed the superiority of cinacalcet in the control of hypercalcemia in CKD patients, and the reduced need for parathyroidectomies in patients who were administered cinacalcet. However, there was no proven benefit on overall mortality in those on cinacalcet (Palmer *et al.*, 2013; Wang *et al.*, 2018).

Despite the evidence to support the use of cinacalcet, the role of total parathyroidectomy in secondary hyperparathyroidism should not be belittled. Evidence shows that although cinacalcet shows significant reductions in iPTH and serum calcium concentrations, its effects are limited to stabilization of mineral bone disease (MBD). In those subjected to parathyroidectomy, their biochemical parameters not only improved, but there was also evidence of restorative changes to the bone evidenced by improvements in bone densitometry (Lilit *et al.*, 2011).

The National Institute for Health and Care Excellence (NICE) have come up with the latest guidelines, and they do not recommend the routine use of cinacalcet in the treatment of secondary hyperparathyroidism in patients with end stage renal disease on dialysis. The use of cinacalcet was only recommended if the serum iPTH levels were persistently elevated and refractory to conventional therapy with vitamin D analogues, or if there were contraindications to parathryoidectomy. The proposed strategies for use of cinacalcet involved high doses of the drug, and it was deemed not cost effective for routine use (National Institute for Health and Care Excellence, 2007). Patients who were refractory to medical therapy, and had symptomatic bone disease, with persistently elevated levels of iPTH were referred for parathyroidectomy.

1.4.2 Surgical Considerations

Surgical indications for parathyroidectomy are not standardized, and vary according to guidelines in different regions. Most guidelines stipulate a certain level of iPTH as a guide to when parathyroidectomy should be performed. A common cut off point is elevation of iPTH levels more than ten times the normal (serum iPTH > 800 pg/ml) (Pitt *et al.*, 2009). However, iPTH level should not be the sole indicator to perform parathyroidectomy as there is no standardized iPTH assay used, and different assays produced a varied result.

Patients who present with symptoms of bone pain, bony deformities, osteoporosis, pathological fractures, and soft tissue calcifications are usually in the advanced stage of bone disease. It would be beneficial if mineral bone disease could be detected earlier to prevent its progress and morbidity. Bone biopsy is the gold standard to confirm the presence of chronic kidney disease – mineral bone disorder (CKD – MBD) (National Kidney Foundation, 2017). However, this practice may not be feasible in all patients due to its invasive, painful nature.

Pre-operative imaging in sHPT is controversial. Most centres do not practice pre-operative imaging as it does not change the operative procedure, nor the surgical outcome. Patients still need to undergo bilateral neck exploration and excision of all 4 hyperplastic glands. Imaging was only recommended in instances where there was recurrent sHPT, which suggested the presence of supernumerary glands, or ectopic

glands. Supernumerary parathyroid glands were found in up to 13% of autopsy specimen, and some report an incidence of up to 30% in patients with sHPT (Pattou *et al.*, 2000). A combination of ultrasonography, CT scan and scintigraphy (MIBI) increased the sensitivity of parathyroid gland detection to 95.4%. Dual modality imaging of ultrasonography and CT yielded sensitivity of 95% (Lee *et al.*, 2015).

With regards to the above, the role of technetium sestamibi scan in secondary hyperparathyroidism is currently limited to recurrent or persistent hyperparathyroidism, where there is failure to identify all 4 parathyroid glands during initial surgery, or due to presence of supernumerary and ectopic glands. In such cases, when scintigraphy confirms presence of an ectopic or supernumerary gland, a CT scan or MRI of the neck should be performed to delineate the anatomy and facilitate dissection during the second surgery (Taïeb *et al.*, 2013).

1.4.3 Surgical Procedure

All patients had undergone surgery under general anaesthesia. Pre-operative insertion of a triple lumen catheter was performed to facilitate the administration of intravenous calcium infusion after complete removal of the parathyroid glands, as well as for monitoring of calcium levels post operatively. Patients were placed in supine position with a sandbag in between the clavicles to better expose the neck region. A collar incision was made and a subplatysmal flap was raised.

We proceeded to dissect up to the thyroid capsule and mobilizing the thyroid gland, displacing it anteriorly and medially after ligation of the middle thyroid vein. The posterolateral aspect of the thyroid gland is examined for any adherent parathyroid glands. The recurrent laryngeal nerve is not routinely identified, but in cases of difficult identification of the parathyroid glands, identifying the recurrent laryngeal nerve might aid in the discovery of the superior parathyroid glands. The superior parathyroid glands may sometimes be seen along the tracheo-oesophageal groove, posterior to the plane of the recurrent laryngeal nerve.

The parathyroid glands are distinguishable from adjacent fat and lymph nodes by its distinctive yellow to tan appearance. In the event that the surgeon was unable to identify the parathyroid gland, a thymomectomy or hemithyroidectomy was performed based on intraoperative findings. Occasionally, cervical lymph nodes were also identified and removed. Upon removal of the final parathyroid gland, IV calcium was administered to

prevent any episodes of life-threatening hypocalcemia. The wound was then closed in layers, opposing muscle and subcutaneous tissue planes with absorbable sutures. The skin was closed subcuticularly with absorbable sutures.

There are debates on methods of parathyroidectomy, whether it should be performed with or without autotransplantation. The main surgical procedures performed for secondary hyperparathyroidism are discussed below in Table 1.1. Each procedure has its benefits and disadvantages. Multiple trials have been done to demonstrate the efficacy of total parathyroidectomy, and meta-analyses shows that it has the lowest rate of recurrence among the three procedures, which translates to a reduced risk of repeat surgery (Li *et al.*, 2017; Liu *et al.*, 2017). However the disadvantages of total parathyroidectomy is the persistent hypocalcemia that follows surgery, requiring lifelong calcium supplementation, not to mention the life-threatening events that may occur following hypocalcemia.

Both subtotal parathyroidectomy and total parathyroidectomy with autotransplantation offer the benefits of functioning residual parathyroid tissue, thus reducing the risk of hypocalcemia. However in the long term, the residual functioning parathyroid tissue may also undergo hyperplasia, rendering the need for further surgery for removal of the residual glandular tissue. Subtotal parathyroidectomy has the advantage that the remnant of the gland keeps its native blood supply, reducing the risk of immediate post operative hypocalcemia. In patients who undergo autotransplantation of the gland in other sites, it may take time to establish a good vascular supply for the remnants of the gland to function. However, in the presence of recurrence, subtotal parathyroidectomy poses difficulties in removal of the gland from its location in the neck and the high risk