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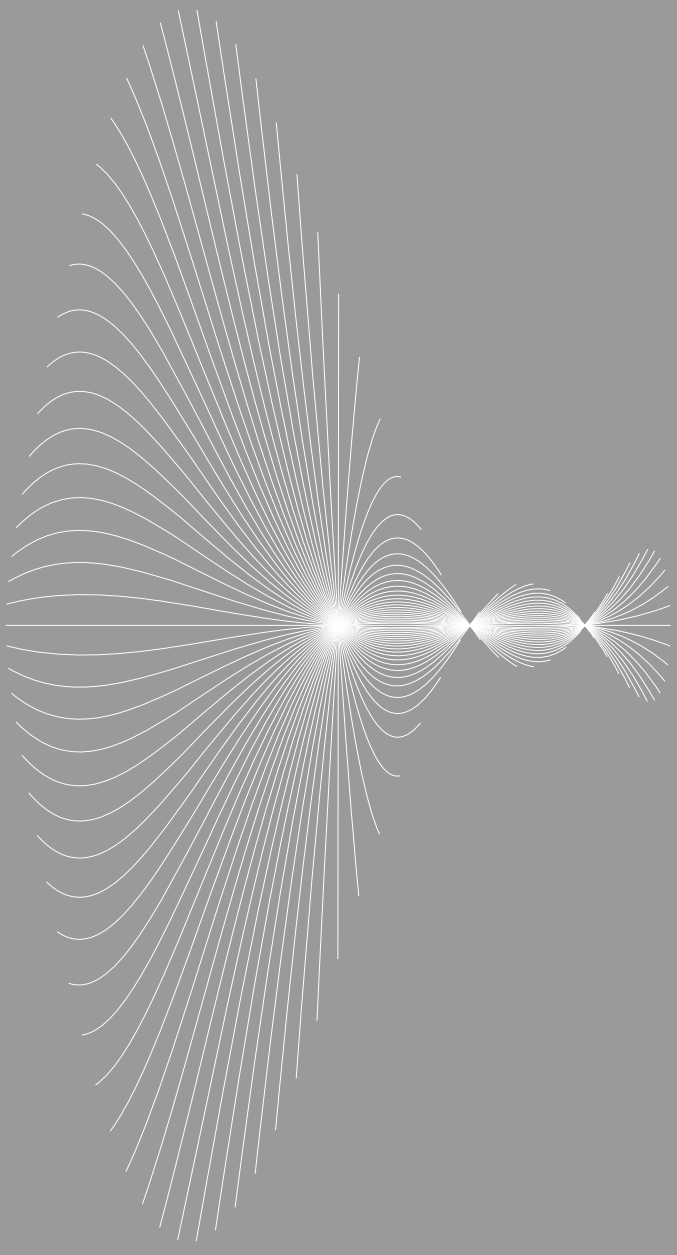
General Introduction



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1. PARATHYROID GLANDS

Anatomy

The parathyroid glands were the last classical endocrine glands to be identified, with the first description made in a rhinoceros by Richard Owen in 1850 (1). The large size of this species probably enabled to macroscopically distinguish the parathyroids from the adjacent thyroid gland (1). Three decades later the parathyroid glands were finally described in humans by Sandström (Figure 1) (1,2). Parathyroid glands vary from 2-7 mm in length, 2-4 mm in width and 0.5-2 mm in thickness (3). Although the majority of normal adults (84%) have 4 glands, 1-7% have 3 glands and 3-13% have 5 glands (4-7). The superior glands arise from the fourth branchial (pharyngeal) pouch and descend into the neck together with the thyroid gland. The superior glands are thus most commonly found near or within the thyroid capsule. The inferior glands, together with the thymus, arise from the third branchial pouch and can be found anywhere from the lower thyroid pole to deep in the mediastinum.

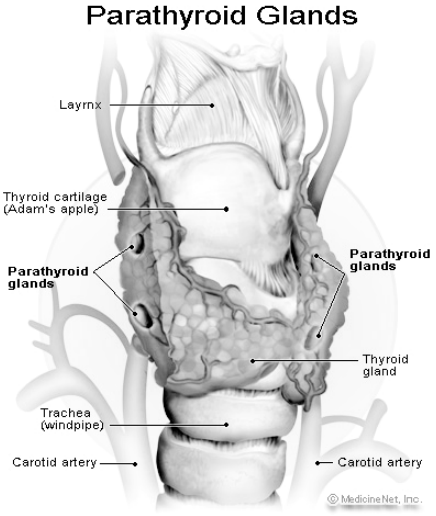

Figure 1: Anatomy of the parathyroid glands

Physiology

The parathyroid glands are essential for normal calcium homeostasis via the production of parathyroid hormone (PTH), which is exclusively produced by the chief cells of the parathyroid glands. PTH production depends on the number of parathyroid chief cells and the secretion of PTH per cell. PTH secretion depends on the setpoint of calcium-dependent secretion, on the secretory capacity of the chief cells and on the number of chief cells that are in the secreting phase. PTH secretion is episodic and rhythmic and once in the circulation, PTH has a very short half life of only a few minutes, enabling very flexible and rapid changes in circulating serum calcium levels. PTH is broken down by Kupfer cells in the liver and PTH fragments are secreted via the kidney together with still intact PTH.

PTH secretion is regulated by extracellular calcium ions, which bind to the calcium sensing receptors (CASR), which are located on the chief cells of the parathyroid gland. Binding of calcium to the CASR activates the receptor, which leads to inhibition of PTH secretion, of *PTH* gene expression and thus PTH synthesis, and of parathyroid cell proliferation (8). PTH secretion is also inhibited by binding of active vitamin D ($1,25(OH)_2D$) to the vitamin D receptor, which is also located in the chief cells of the parathyroids.

In contrast, hypocalcaemia results in a release of available PTH from its intracellular reservoir, in a decrease in intracellular break down of PTH, in a increase of PTH biosynthesis and in a decrease of the secretory rest phase of the parathyroid cell (9). Long-term hypocalcaemia eventually results in four-gland parathyroid hyperplasia.

Pathophysiology of hyperparathyroidism

Hyperparathyroidism is the disease state resulting from one or more parathyroid glands producing too much PTH. This disease state is associated with an increase in the calcium-dependent setpoint of PTH secretion, an increase in the number of PTH secreting cells and an increase in parathyroid parenchymal cells.

Hyperparathyroidism can be secondary to a decrease in serum calcium concentration caused by a negative calcium balance, due to vitamin D deficiency,

renal insufficiency, gastro-intestinal disorders, or hypercalciuria of renal origin. Long-term stimulation of the parathyroids by persistent hypocalcaemia is eventually associated with monoclonal changes, resulting in autonomous "tertiary" hyperparathyroidism. In this case the production of PTH is no longer regulated by circulating serum calcium concentrations, which is analogous to the case in primary hyperparathyroidism.

In primary hyperparathyroidism (PHPT) one or more parathyroid glands are by definition autonomous. The increase in the calcium-dependent setpoint of the chief cells, leads to increased PTH secretion despite increased levels of serum calcium (Figure 2). The most important determinant of the calcium-dependent setpoint for PTH secretion is the number and function of CASR. Although, mutations in the *CASR* gene and downregulation of CASR expression, have been described in 31% of parathyroid carcinomas, the majority of patients with PHPT have normal expression and function of the CASR (10,11).

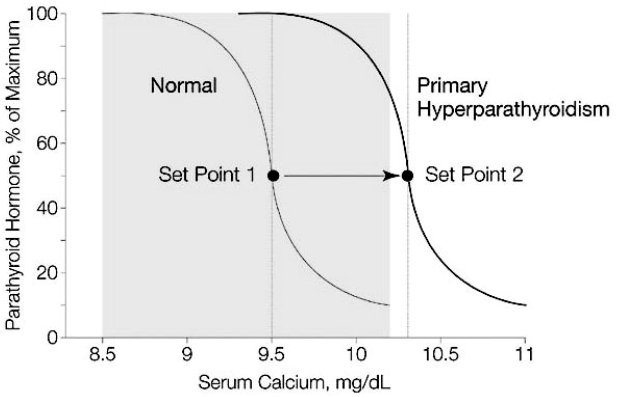

Figure 2: Changes in the calcium-dependent setpoint leading to PHPT

II. PRIMARY HYPERPARATHYROIDISM

Incidence

The estimated incidence of PHPT is 0.4% in adult men, 1.7% in adult women and 2-3% in women above the age of 60 years (12-14).

Clinical features

Over the past few decades, the clinical profile of PHPT, originally described as "bones, stones, groans and psychic moans", has drastically changed to an almost asymptomatic disease, due to the introduction of automated calcium screening. Chronic exposure of the skeleton to high circulating PTH concentrations increases bone turnover in favour of bone resorption, ultimately leading to decreased bone mineral density, predominantly at cortical sites, and increased risk of fractures. PTH has been shown to influence bone metabolism by stimulating RANKL secretion, an osteoclast activator, and by suppressing OPG secretion, the natural decoy receptor for RANKL (15-25).

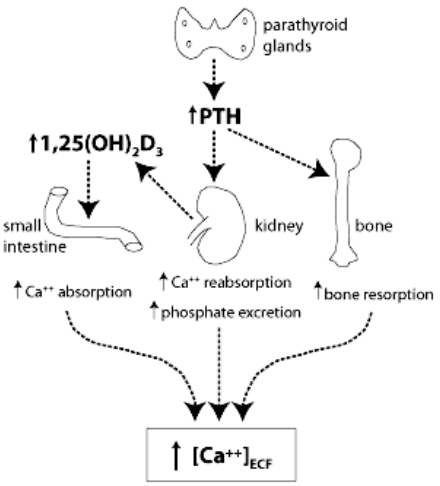

Figure 3: The effect of increased PTH concentrations on bone, kidney and intestine

In the kidney, high circulating PTH levels increase tubular reabsorption of calcium and decrease tubular reabsorption of phosphate. However, approximately 30% of patients with PHPT demonstrate hypercalciuria, with increased risk for nephrocalcinosis and nephrolithiasis. Renal function may deteriorate due to hypercalcaemia and associated dehydration and to recurrent renal stones. PTH also stimulates 1α-hydroxylase enzyme synthesis in the kidney, which is essential for the

conversion of 25-hydroxyvitamin D, into its active metabolite, 1,25-dihydroxyvitamin D. Active vitamin D stimulates the intestinal absorption of calcium.

The net result of increased circulating PTH concentrations on bone, kidney and intestine is an increase in extracellular serum calcium concentration. Clinical manifestations of hypercalcaemia include polyuria, polydipsia and constipation. Hyperparathyroidism may also be associated with non specific symptoms, such as tiredness, mood swings, depression, irritability, forgetfulness, bony pain and muscle weakness.

Pathological changes

Primary hyperparathyroidism can most commonly occur sporadically or more rarely in the context of a genetic syndrome, such as MEN-I (OMIM 131100), MEN-IIa (OMIM 171400) or hyperparathyroidism-jaw tumor (HPT-JT; OMIM 607393) (26). The disease is caused by a solitary parathyroid adenoma in more than 80% of cases, hyperplasia in 15-20% of cases and parathyroid carcinoma in 0.1 to 5% of cases (27-31).

A parathyroid adenoma is characterized by the presence of an encapsulated benign neoplasm usually involving a single gland with an adjacent rim of normal glandular tissue (32).

Parathyroid hyperplasia is characterized by an absolute increase in parathyroid parenchymal cell mass resulting from proliferation of chief cells, oncocytic cells and transitional oncocytic cells in multiple parathyroid glands in the absence of a known stimulus for PTH hypersecretion such as renal failure or vitamin D deficiency (32). A diagnosis of hyperplasia is also favoured when synchronous multiglandular disease is found at surgery.

Parathyroid carcinoma is a malignant neoplasm derived from parathyroid parenchymal cells, which, according to the criteria of the World Health Organization, is characterized by vascular invasion, perineural space invasion, capsular penetration with growth into adjacent tissues and/or metastases (32). The

presence of a trabecular pattern, fibrous bands and/or multiple mitoses are considered to be only minor diagnostic criteria.

Localization studies

Localization studies are not required in case of traditional bilateral neck exploration, because experienced surgeons have an 86–100% chance of excision of all pathological tissue as the procedure entails visualization of all four parathyroid glands (33,34). However, localization studies become mandatory when a more focused unilateral or minimally invasive approach is opted for.

Technetium 99m sestamibi (Tc99m-MIBI), particularly when complemented with single emission computed tomography (Tc99m-MIBI-SPECT), is currently the imaging technique of choice for the preoperative localisation of parathyroid adenomas (33,35). Tc99m-MIBI is a monovalent lipophilic cation that diffuses passively through cell membranes and accumulates almost exclusively in mitochondria following negative membrane potentials (36). In primary hyperparathyroidism, the increased uptake of Tc99m-MIBI is based on an abundance of mitochondria in parathyroid oxyphil cells, which sequester sestamibi intracellularly, and on increased perfusion of hyperactive parathyroid glands. The sensitivity of Tc99m-MIBI-SPECT for localising hyperactive parathyroid glands ranges from 66% to 90% and the positive predictive value ranges from 83 to 100% (33,37-44).

In experienced hands, an ultrasound (US) of the neck is a highly sensitive technique, which is more convenient and less expensive than Tc99m-MIBI-SPECT and particularly more sensitive for intrathyroidally located parathyroids, which is a difficult location for other non-invasive localization techniques. US, however, is of limited value in the case of retrosternal or posteriorly located parathyroid glands. The reported sensitivity is highly variable, ranging from 47% to 89%, depending on parathyroid pathology and the presence of thyroid nodules (33,45-48).

The use of Computed Tomography (CT)-scans and of Magnetic Resonance Imaging (MRI)-scans is recommended in the case of a suspected ectopic mediastinal parathyroid gland, to better define size and location of the lesion

relative to adjacent structures (49). The sensitivity of CT-scans for localising hyperactive parathyroid glands remains, however, lower than that of Tc99m-MIBI-SPECT and US, despite recent developments in equipment and in diagnostic protocols and algorithms (45). A very promising localization method is the novel four-dimensional CT scan (4D-CT), which provides both functional and highly detailed anatomic information about parathyroid tumors. This method is reported to have a sensitivity of 70% for localising hyperactive parathyroid glands (50). MRI is time-consuming, expensive, difficult to interpret and a number of patients cannot undertake the procedure because of indwelling pacemakers and other metallic implants (51).

Selective venous sampling (SVS) of parathyroid hormone (PTH) is an invasive technique that can be used when the above mentioned noninvasive localization studies are negative or disconcordant. During SVS a catheter is introduced under local anaesthesia via a sheath in the right femoral vein by an intervention radiologist and is guided by fluoroscopy to each of the jugular, subclavian and brachiocephalic veins, the azygos vein and to the vena cava superior and inferior, from which serial blood samples are obtained for PTH measurement. SVS is based on the anatomical assumption that regional drainage of each parathyroid gland occurs via the veins of the thyroid plexus into the adjacent superior, middle and inferior thyroid veins (52). However, there are many variations in the venous anatomy of the parathyroid glands due to embryological differences, but most often also due to previous surgical interventions disturbing local anatomy and venous drainage. Despite these anatomical variations, SVS has been reported to be successful in predicting the side of a pathological parathyroid gland in 39-93% of patients with primary hyperparathyroidism (49,52-60) and in 66-75% of patients with negative noninvasive studies (57,58,61). SVS is also successful in identifying the anatomical location of an ectopic parathyroid gland, with a sensitivity 66-100% (62,63).

Management of primary hyperparathyroidism

In primary hyperparathyroidism (PHPT), surgical removal of all pathological parathyroid glands is the only approach that provides definitive and durable cure.

Cure rate is 94-100% for bilateral neck as well as less invasive surgery, more than 6 months after parathyroidectomy (PTx) (33,38,40-44,64-66) with a complication rate of 0.4%-7.7% in the hands of experienced surgeons (41,43,44,65,66). The risks of surgery for PHPT consist in 13-20% of patients in hypoparathyroidism, in 1-6% of patients in transient or permanent vocal cord damage due to unilateral or bilateral damage to the nervus laryngeus recurrens and in <1% to mortality.

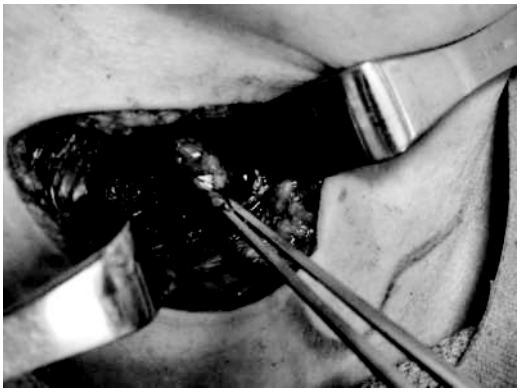

Figure 4: Resection of an enlarged parathyroid gland during minimally invasive neck surgery

Surgery can be performed by standard bilateral neck exploration, which consists of visualization of all four parathyroid glands followed by either excision of a single enlarged parathyroid gland, or subtotal or total parathyroidectomy with auto transplantation if more than one parathyroid gland is found to be enlarged.

Unilateral neck exploration and minimally invasive neck exploration both require pre-operative localization of the enlarged parathyroid gland and the use of intra-operative PTH (IOPTH) measurement to predict that the pathological parathyroid tissue has been fully excised. The "Miami criteria" are used to interpret IOPTH measurement: a PTH decrease of more than 50% after excision of all pathological parathyroid tissue (67,68). If the IOPTH does not drop below 50% or if a pathological gland is not found during minimally invasive surgery, the procedure is conversed to bilateral neck exploration. IOPTH monitoring has a sensitivity of up

to 99% (69,70) and has been shown to significantly increase cure rate by about 10% (69,71).

Cinacalcet is the only registered medical treatment for PHPT and is available for clinical use in the Netherlands since the summer of 2009. Cinacalcet is a calcimimetic approved by the European Medicines Agency Committee for Medicinal Products for Human Use for "the reduction of hypercalcaemia in patients with primary hyperparathyroidism for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by the relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated" (72). Calcimimetics increase the sensitivity of the calcium sensing receptor (CASR) on parathyroid cells to extracellular calcium concentration (73-79), thereby significantly decreasing serum PTH and calcium concentration. This agent has been reported to normalize serum calcium concentration in ~88% of patients with PHPT (76-79).

Fate of complications after successful surgery

In PHPT, the importance of achieving cure has been highlighted in a number of studies focusing on the effect of parathyroidectomy on bone mineral density, nephrolithiasis and neurocognitive function (80-82). Patients who are cured after PTx demonstrate a significant postoperative increase in bone mass, with BMD remaining significantly higher than baseline values for up to 15 years after parathyroidectomy (81-83). This is in contrast to patients treated conservatively, in whom significant cortical bone loss and increased fracture risk is observed in the long-term. As reported in a number of published studies, patients with nephrolithiasis at presentation demonstrate no recurrence of renal stones after successful PTx, in contrast to a 75-100% chance of recurrent nephrolithiasis in conservatively treated patients (80,83). Symptomatic and also "asymptomatic" patients undergoing parathyroidectomy have also been reported to experience a significant improvement in various parameters of quality of life compared to patients who did not have surgery (84-88).

III. PERSISTENCE OR RECURRENCE OF PHPT

Definitions

Persistence of hyperparathyroidism is defined as high serum calcium and PTH concentrations or inappropriate concentrations of one parameter with respect to the other, documented directly post-operatively or within the first 6 months after parathyroidectomy, and persisting thereafter. Recurrence of hyperparathyroidism is defined as the recurrence of elevated serum calcium and PTH concentrations after successful PTx and a period of normalization of both parameters of at least 6 months after surgery.

Etiology

Persistent hyperparathyroidism is reported to occur in 2-7% of patients after parathyroidectomy (33,89,90). Excluding insufficient experience of the operating surgeon, persistent PHPT may be caused by a pathological gland which is missed during initial surgery (6.3-69%), a second adenoma (6.3%), non-recognition or incomplete excision of multiple gland hyperplasia (9-29%), an ectopically located hyperactive gland undetected at initial surgery (11-77%), supernumerary glands (4.2-8%) or rarely parathyromatosis from parathyroid cell spillage during initial surgery (0.7-6.3%) (90-98). The diagnosis of persistent hyperparathyroidism may be delayed because of initial suppression of multiple pathological glands by a dominant enlarged gland, falsely suggesting cure immediately post-operatively. These pathological glands eventually overcome their suppressed state leading to overt hyperparathyroidism.

In a 5 year follow-up of 91 patients successfully operated for PHPT, Westerdahl *et al* reported a recurrence rate of hyperparathyroidism of 4%, largely due, however, to previously undiagnosed germline mutations in the *MEN-1* gene and, consequently, multiple gland pathology (99). Other causes of recurrence of PHPT are metastases from a parathyroid carcinoma or newly developed adenomas, most of the times arising in hyperplastic parathyroid glands (91-93).

Location of ectopic parathyroid glands

In 24-77% of patients who undergo revision surgery for PHPT missed glands are found in ectopic locations, such as the tracheoesophageal groove (2.8-33%), thymus (8.3-27%), retroesophageally (1.8-10.4%), intrathyroidally (4-10%), the carotid bifurcation (8.3%), the mediastinum (2.6-7.3%), the aortic-pulmonary window (1.3-6.3%), the carotid sheath (2.1-5.5%) and parapharyngeally (2.1%) (56,93,94,100,101).

Most ectopias of the superior gland are acquired ectopias due to the effect of gravity on an enlarged gland, causing the gland to travel down the prevertebral plane towards the posterosuperior mediastinum (102). Congenital ectopias of the superior glands, are due to undescended glands, found behind the pharynx, above the superior thyroid pole or at the posteromedial aspect of the thyroid lobe, while an excessively migrated gland can be found intrathyroidal (102). Most inferior gland ectopias are congenital ectopias caused by abnormal embryological migration of the parathymic complex, extending from the angle of the mandible to the pericardium (102). An undescended inferior parathyroid gland can be found along the carotid sheath, from the angle of the mandible to the lower thyroid pole (103), while an excessively migrated gland can be found in the anterior mediastinum, within the thymus or at the posterior aspect of the thymic capsule.

Supernumerary glands develop from accessory parathyroid fragments caused by the rapid caudal and medial migration of the thymus, which may drag a fragment of the third branchial pouch, the origin of the inferior parathyroid glands (102). Supernumerary glands may also be found in close contact with the vagus nerve or sometimes within it (104). There is a close spatial relationship between the vagus nerve and the third and fourth pharyngeal pouches, the origin of the inferior and superior parathyroid glands, as a portion of this nerve is derived from the fourth branchial arch.

Localization studies

A second (or subsequent) neck exploration is technically more challenging than initial surgery and may be associated with an up to 3-fold increase in morbidity

(33,93,105,106). Localization studies are, therefore, highly recommended prior to revision surgery in order to decrease operation time, improve surgical outcome and reduce the risk of complications due to lengthy surgical explorations (33,91,93,105,106).

The sensitivity of Tc99m-MIBI-SPECT prior to revision surgery varies from as low as 27% to as high as 94%, depending on the selection of patients, the pathology of the parathyroid gland(s) and the methods used to determine the accuracy of the technique (49,94,96,97,100,101,107-111). Tc99m-MIBI-SPECT has a lower sensitivity in patients with multiple hyperplastic parathyroid glands compared to patients in whom a single adenoma is found at surgery (94% vs. 43%) (112). The sensitivity of Tc99m-MIBI-SPECT is also decreased in patients who have had previous resection of pathological parathyroid gland(s) compared to patients who have had previous negative neck exploration (89% vs. 27%) (108).

Ultrasound of the neck (US) is reported to have a sensitivity of 17%-90% prior to revision surgery (49,94,96,97,101,107,108,110-113). In contrast to Tc99m-MIBI-SPECT, US is not influenced by the pathology of the parathyroid gland (112).

When both Tc99m-MIBI-SPECT and US are negative or when results of these localisation techniques are disconcordant, an MRI-scan, CT-scan or selective venous sampling for PTH (SVS) can be helpful to identify residual pathological parathyroid gland(s). The sensitivity of MRI-scan prior to revision surgery is 33-89% (49,97,110-112), that of CT-scan is 33-50% (49,97,110) and that of SVS is 50-91% (49,94,97,111,114). 4D-CT has shown a promising sensitivity of 80% prior to revision surgery in patients with PHPT who have had previous unsuccessful parathyroidectomy (108).

Outcome of revision surgery

Despite the challenges of revision surgery, the reported cure rate remains high after re-exploration ranging from 82% to 100% (49,56,94,96,100,101,107-109,111,115,116). However, the highest cure rates (98-100%) are found in patients who had previous thyroid surgery or negative neck explorations and in patients who have solitary adenomas (101,109,115) and the lowest cure rates (82-83%) are found

in patients with persistent hyperparathyroidism after removal of one or more pathological parathyroid glands (94,108). Patients with multiple gland hyperplasia and patients who have had 3 previous neck explorations are less likely to achieve cure after further surgery (96,107).

Complications of revision surgery

Re-operations are associated with an increased risk of complications due to distortion and scarring of surgical planes caused by previous interventions. The overall complication rate after revision surgery is reported to be none to 29% (49,56,94,96,101,107,108,117,118). The most common complications are hypoparathyroidism (2.6-12.9%) and permanent or transient recurrent laryngeal nerve injury (0.08-25% and 2.3-13.5%, respectively) (49,56,94,97,100,101,107,111,117-119). Other possible complications are post-operative bleeding requiring blood transfusion (1.1-2.1%), mandibular nerve injury (0.4-1.6%), wound hematoma (0.08-2.2%), pneumothorax (1.6-4.4%), pneumonia (0.4%-2.2%) and deep venous thrombosis or pulmonary embolism (1-2.2%) (56,94,100,101,108,117). Rare complications are Horner syndrome after sternotomy, chylous fistulas, arrhythmia, myocardial infarction, wound erythema and renal failure (56,108,117).

IV. OUTLINE OF THIS THESIS

Part I. Cure after parathyroidectomy for primary hyperparathyroidism

Primary hyperparathyroidism is the most common cause of hypercalcaemia in the outpatient setting. Surgical removal of all pathological parathyroid glands is the only approach that provides definitive and durable cure in these patients. Patients who are cured after surgery show a significant postoperative increase in bone mass (81-83), no recurrence of renal stones (80,83) and improvement in various parameters of quality of life compared to patients who had no or unsuccessful surgery (84-88). In ***Chapter 2*** we assessed the prevalence of persistent and recurrent hyperparathyroidism after surgery for primary hyperparathyroidism in our hospital

over a 24 year period. We also evaluated the fate of clinical symptoms and complications of PHPT after successful surgery.

Part II. Localization studies in persistent primary hyperparathyroidism

The need for preoperative localization of pathological parathyroid gland(s) before initial surgery depends on the chosen surgical approach. In case of traditional bilateral neck exploration localization studies are not deemed necessary, but they become mandatory prior to more focused unilateral or minimally invasive surgery (33,34). Accurate localization studies are even more important before revision surgery for persistent hyperparathyroidism, as a second (or subsequent) neck exploration is technically more challenging than initial surgery (33,93,105,106). In ***Chapter 3*** we evaluated the predictive value of Tc99m-MIBI-SPECT in patients with persistent PHPT prior to revision surgery compared to the predictive value of this technique in patients with sporadic PHPT prior to initial surgery.

We also evaluated the predictive value of selective venous sampling for PTH in patients with persistent PHPT prior to revision surgery compared to the predictive value of Tc99m-MIBI-SPECT in the same patient group. Results of this study are described in ***Chapter 4***.

Part III. Complications of the surgical management of primary hyperparathyroidism

PHPT is associated with decreased bone mineral density, due to the stimulating effects of increased circulating levels of PTH on osteoclastogenesis by the stimulation of RANKL secretion, an osteoclast activator, and the suppression of OPG secretion, the natural decoy receptor for RANKL (15-25). The increased bone turnover in favour of bone resorption induced by the pre-operative hyperparathyroid state, leads to demineralization of bone particularly at cortical sites. Following successful surgery, the rapid decrease in serum PTH levels and the pre-operative high bone turnover state, lead to a transient hypocalcaemia, due to increased influx of calcium, phosphate and magnesium into bone. Restoration of mineralization of

bone and eventual decrease in bone turnover lead to a significant increase in bone mass (81-83).

Post-operative severe persistent hypocalcaemia is usually due to a hungry bone syndrome, a syndrome seldom seen in patients with sporadic PHPT. The syndrome is predominantly observed in patients with severe hyperparathyroidism-associated increased bone turnover, specially those with parathyroid carcinoma. Data on this rare complication of the treatment of primary hyperparathyroidism are scarce and its management remains a challenge. In ***Chapter 5*** we performed a systemic review of the literature on hungry bone syndrome, summarizing its main features and suggestions for its prevention and management.

Part IV. Aspects of osteocyte function in primary hyperparathyroidism

Some of the effects of PTH on bone are exerted by the specific binding of PTH to its receptor PTHR1 in osteocytes, resulting in inhibition of the expression of the *Sost* gene (120-123). This gene encodes for the protein sclerostin, which decreases bone formation by inhibition of the Wnt signaling pathway in osteoblasts (124,125). Intermittent PTH administered to post-menopausal women has been shown to decrease circulating sclerostin levels (126). To assess whether chronic hypersecretion of PTH also inhibits sclerostin secretion, we measured serum sclerostin concentrations in patients with untreated PHPT and in patients cured after successful parathyroidectomy for PHPT. Results are reported in ***Chapter 6.***

Binding of PTH to the PTHR1 on osteocytes has been reported to upregulate Fibroblast Growth Factor 23 (FGF23) mRNA production (127,128), a stimulator of tubular phosphate transport and a suppressor of 1α-hydroxylase production by the kidney (129,130). Reports on the effect of chronic high circulating levels of PTH, as characteristic of PHPT, on FGF-23 levels are scarce and not always concordant (130-132). In ***Chapter 7*** we evaluated the effect of chronic excess of PTH on FGF23 concentrations by measuring FGF23 concentrations in patients with PHPT before surgery and in those with euparathyroidism cured after successful parathyroidectomy for PHPT.

Part V. Clinical and molecular aspects of parathyroid carcinoma

In ***Chapter 8*** we report the many challenges and pitfalls encountered in the management of a patient with multiple metastases from parathyroid carcinoma over a 17 year period.

Several genes have been discovered to play a role in the etiology of PHPT, among which the *MEN-1*, *HRPT2* and *CASR* genes. Mutations in the *HRPT2/CDC73* gene, which encodes for the protein parafibromin (133), are associated with the hyperparathyroidism-jaw tumor syndrome (HPT-JT; OMIM 607393). Patients with a HPT-JT syndrome have a 15-24% chance of developing parathyroid carcinoma (29,134-136) and loss of heterozygosity of chromosome 1q, the location of the *HRPT2/CDC73* gene, is reported to be found in 55% of parathyroid carcinomas (1,17,19-21). Downregulation of the CASR has been reported in patients with the HPT-JT syndrome, as well as in patients with sporadic carcinoma (137).

The aim of the study described in ***Chapter 9*** was to evaluate the role of mutations in the *HRPT2/CDC73* gene, loss of parafibromin staining or downregulation of CASR expression as determinants of prognosis in patients with an established diagnosis of parathyroid carcinoma.

Part VI. Management of patients with persistent primary hyperparathyroidism

In patients with persistent primary hyperparathyroidism who had undergone multiple surgeries, re-explorations are associated with a more than 3-fold increased risk of morbidity (33,93,105,106), due to scarring of the operation field and disruption of the normal patterns of drainage by previous surgeries. In ***Chapter 10*** we assessed the demographic, clinical, biochemical, surgical and pathological characteristics of patients with persistent PHPT to identify predictive factors for cure after revision surgery.

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