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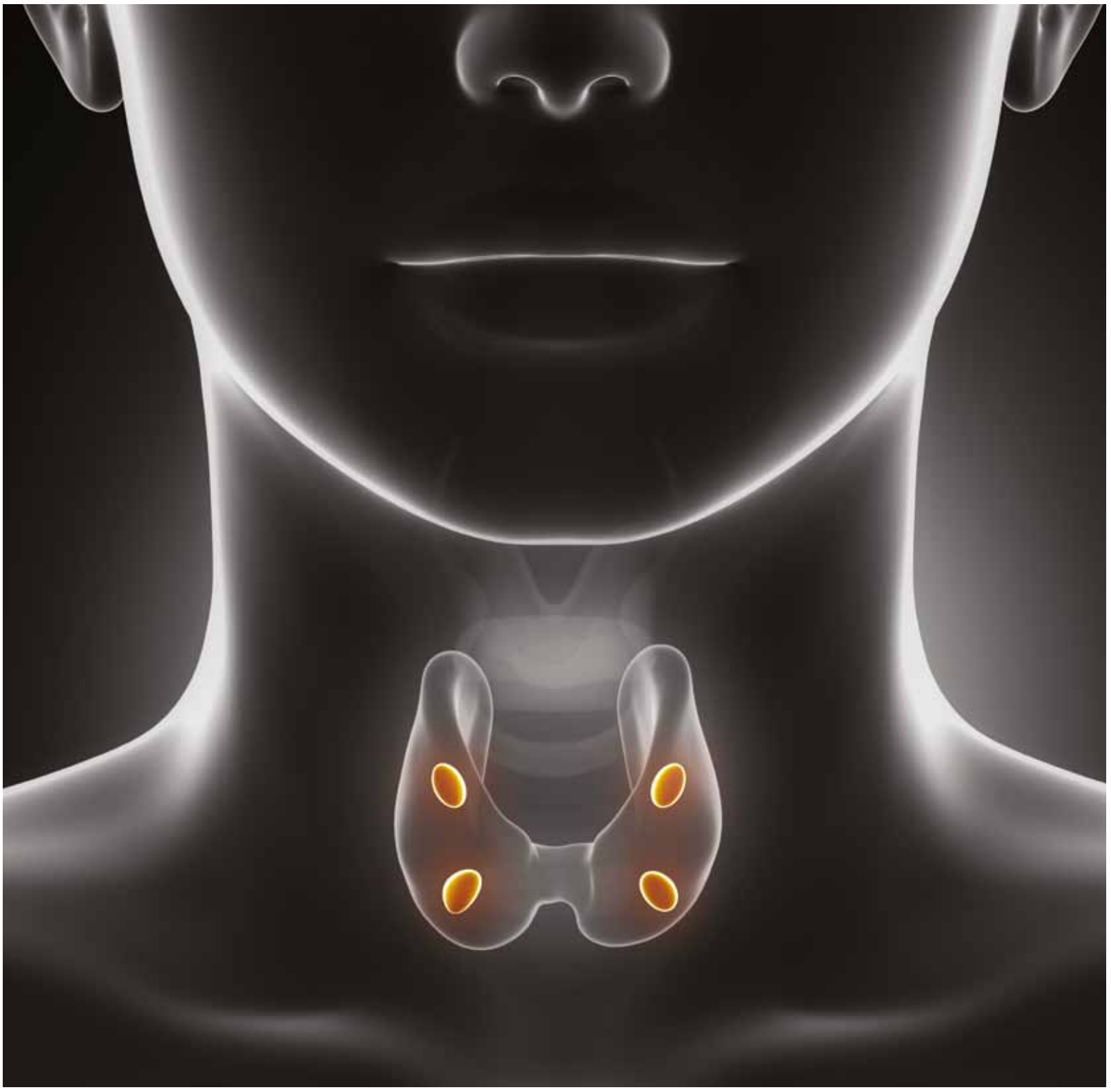

Primary hyperparathyroidism

Introduction

HYPERCALCAEMIA is frequently encountered in practice. The differential diagnosis of hypercalcaemia is quite broad; however, primary hyperparathyroidism remains the most common cause of hypercalcaemia in the non-hospitalised patient, affecting on average 25-60 individuals per 100,000. The incidence of the disease increases with age, with females 2-3 times more likely to be affected than males.

Classic signs and symptoms of severe primary hyperparathyroidism in the developed world are now mainly of historical interest. Osteitis fibrosa cystica, severe bone loss, severe peptic ulcer disease, nephrocalcinosis, gout and pseudogout are now rarely manifested in patients with primary hyperparathyroidism. More commonly, patients who are symptomatic will exhibit less dramatic variations of the classically taught symptoms of 'bones, groans, stones and moans' — that is painful bones, abdominal groans, kidney stones and psychiatric overtones. Recent evidence also suggests acceleration of cardiovascular disease in patients with moderate-to-severe disease.

There exists no debate that patients with biochemically proven primary hyperparathyroidism who exhibit symptoms of hypercalcaemia will benefit from surgical management, which remains the only definitive cure for the condition. With the advent of the serum-screening chemistry panel, however, up to 80% of patients with primary hyperparathyroidism are diagnosed incidentally and are considered asymptomatic. It is in this cohort where questions arise regarding the potential for surgical and medical management of their disease.

This article will review the diagnosis, investigation and management of primary hyperparathyroidism.

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Pathophysiology

THE differential diagnosis of hypercalcaemia is quite broad, as summarised in table 1. In primary hyperparathyroidism, hypercalcaemia results from overproduction of parathyroid hormone (PTH). The parathyroid glands are a set of four endocrine organs located on the posterior surface of the thyroid gland. The principal function of the glands is maintenance of serum calcium homeostasis through a simple and potent negative feedback loop. Decreased levels of serum calcium will stimulate the parathyroid glands to increase PTH secretion. PTH exerts its effects primarily on the bones and kidneys by stimulating calcium release and reabsorption, respectively. PTH will also stimulate the synthesis of 1,25-dihydroxyvitamin D — the active form of vitamin D — to, in turn, stimulate gut reabsorption of calcium. In primary hyperparathyroidism, hypercalcaemia is a result of either one or potentially multiple autonomously active glands.

Table 1: Differential diagnosis of hypercalcaemia

Primary hyperparathyroidism
Malignancy
Chronic granulomatous disease
Familial hypocalciuric hypercalcaemia
Endocrine disorders
Medication
Dietary intake
Prolonged immobilisation

Clinical features

History

ANY evaluation of a patient with suspected primary hyperparathyroidism should begin with a thorough history and physical examination. Specific questions should be aimed at identifying target-organ effects of hypercalcaemia, such as a history of nephrolithiasis, chronic constipation, fragility fractures, pancreatitis, gouty arthritis and peptic ulcer disease.

Medications that contain calcium, affect calcium homeostasis or affect PTH secretion should be carefully reviewed. Such medications include calcium-containing antacids, vitamin D supplements, thiazide diuretics and lithium.

Coexisting thyroid pathology is common in primary hyperparathyroidism; thus, any history of prior head and neck irradiation should be elucidated when considering potential thyroid malignancy.

Along with the classic and easily identifiable signs and symptoms of hyperparathyroidism, a myriad of subtle neurocognitive complaints are seen in primary hyperparathyroidism. Patients will frequently complain of fatigue, weakness, depression or memory impairment.

Finally, a thorough family history should be obtained, particularly in younger patients with the condition. A family history of pituitary or endocrine pancreatic neoplasms is suggestive of type I multiple endocrine neoplasia (MEN) syndrome. Other syndromic forms of primary hyperparathyroidism include MEN 2, MEN 4, hyperparathyroid–jaw tumour syndrome and familial hypocalciuric hypercalcaemia.

Familial hypocalciuric hypercalcaemia is a benign, autosomal-dominant condition resulting from a heterozygous mutation of the calcium-sensing receptor gene. The condition can be easily excluded by measurement of 24-hour urinary calcium level. Urinary calcium levels less than 100mg over 24 hours or a serum-calcium-to-creatinine clearance ratio less than 0.01 are indicative of the diagnosis. This can be confirmed by genetic testing. These individuals should be identified prior to surgery because such patients do not benefit from parathyroidectomy.

Physical examination

Physical examination should include a detailed evaluation of the neck — from mandible to sternum. Looking carefully for scars will provide clues to clinicians of prior operations the patient may have omitted to mention in their history. This is especially important because prior surgery may alter the surgical approach.

The thyroid gland should be palpated to assess for nodules that may require ultrasound and fine-needle biopsy.

An examination of the cervical nodal basins should also be included in every examination.

Investigations

Pathology tests

TO establish a diagnosis of primary hyperparathyroidism, one needs to demonstrate elevated or non-suppressed levels of PTH in the setting of hypercalcaemia.

Calcium

Any test result showing elevated serum calcium should be repeated. A measurement of serum albumin should be included to calculate a corrected calcium concentration, as 40% of circulating calcium is bound to the protein.

The additional testing of ionised calcium levels is likely unnecessary if the diagnosis of hypercalcaemia is confirmed. Ionised calcium level testing may be of use, however, in patients with chronic acid–base disorders.

Furthermore, up to 10% of patients with primary hyperparathyroidism with normal corrected calcium levels will have elevated ionised calcium levels.

Such patients remain classified as hypercalcaemic.

PTH

The intact PTH molecule is an 84-amino-acid peptide. Early attempts at developing assays for measuring PTH levels were limited by the molecule's extremely low circulating concentration (10-65pg/mL) and half-life (2-4 minutes). Furthermore, hepatic and renal metabolism of PTH results in circulating amino-terminal and carboxy-terminal fragments. At times when PTH release is suppressed, the parathyroid gland may secrete carboxy-terminal fragments of the hormone. This heterogeneity of circulating hormone made first-generation PTH assays unreliable. Second-generation PTH assays have a greater specificity for the intact PTH molecule but still frequently cross-react with larger fragments. The newest third-generation ('bio-intact') assay shows the greatest specificity for the fully intact hormone with the added advantage of detecting a post-translational modified form of PTH (N-PTH), known to represent up to 10% of circulating PTH in normal individuals. N-PTH levels may be higher in individuals with parathyroid carcinoma or severe primary hyperparathyroidism. However, despite the stated advantages of the third-generation assay, head-to-head comparisons between second- and third-generation assays are limited.

As a result of the prevalence of vitamin D insufficiency and its potential to worsen the prognosis of primary hyperparathyroidism, it is recommended to check 25-hydroxyvitamin D levels in all patients with the condition.

Vitamin D

Vitamin D insufficiency is quite common in primary hyperparathyroidism. Inadequate levels of vitamin D (25-hydroxyvitamin D level less than 50nmol/L) can accelerate end-organ damage in the condition. Patients with primary hyperparathyroidism who have vitamin D insufficiency have also been found to have lower bone mineral density (BMD) at the femoral neck and distal radius. In turn, the level of the active vitamin D metabolite 1,25-dihydroxyvitamin D in patients with the condition is often elevated because of the increased conversion of the inactive form.

As a result of the prevalence of vitamin D insufficiency and its potential to worsen the prognosis of primary hyperparathyroidism, it is recommended to check 25-hydroxyvitamin D levels in all patients with the condition. Additional testing of 1,25-dihydroxyvitamin D levels is not routinely recommended.

Vitamin D replacement should be initiated cautiously in patients with primary hyperparathyroidism. Serum calcium and urinary calcium excretion should be monitored to ensure no worsening of hypercalcaemia or risk of nephrolithiasis with initiation of therapy. The goal of replacement should be to normalise serum 25-hydroxyvitamin D levels between 50-75nmol/L. Although vitamin D repletion will result in a lowering of PTH levels, it is our opinion that vitamin D replacement should not delay localisation imaging or referral for definitive surgical management.

Additional laboratory testing

Once the diagnosis of primary hyperparathyroidism is suspected, additional laboratory testing should be performed to gauge end-

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organ dysfunction. A thorough biochemistry panel is often done hand-in-hand with serum calcium measurements. Such panels should include measurements of phosphate, alkaline phosphatase, blood urea nitrogen and creatinine.

An accurate estimation of creatinine clearance is essential, as renal insufficiency will lead to increased PTH secretion — thus accelerating bone loss. Further assessment of renal disease should include a 24-hour urine test to calculate urinary calcium and exclude familial hypocalciuric hypercalcaemia.

Imaging

Abdominal assessment

In their most recent guidelines for management of asymptomatic primary hyperparathyroidism, a panel of experts has recommended routine abdominal imaging in the form of ultrasound, X-ray, or CT to exclude renal stones or nephrocalcinosis — an often asymptomatic extracellular deposition of calcium crystals within the renal parenchyma.

Skeletal assessment

Skeletal assessment for patients with suspected primary hyperparathyroidism begins with bone mineral densitometry. Bone mineral densitometry by dual-energy X-ray absorptiometry (DXA) is recommended at the hip, lumbar vertebra and distal radius. As PTH predominantly affects cortical bone, bone mineral densitometry at the distal radius is especially important. Nevertheless, fracture incidence in primary hyperparathyroidism is increased at both cortical and trabecular (vertebral) sites.

Additional means of assessing skeletal involvement include vertebral fracture assessment, which will detect vertebral fracture by DXA. Vertebral fracture assessment is a useful adjunct, especially in light of the fact a majority of patients with vertebral fracture are asymptomatic, and up to 40% of patients will have BMD T-scores better than -2.5 — the WHO cut-off for defining osteoporosis.

Localisation studies

The utility of localisation studies is solely for the purpose of operative planning. The ability to successfully localise a parathyroid adenoma should not alter the decision to pursue operative or non-operative management. Localisation studies are extremely useful, however, in guiding the surgeon in deciding the extent of operation and in elucidating ectopically placed glands. Several imaging modalities are at the clinician's disposal; however, the mainstays remain ultrasound and nuclear scintigraphy. In recent years, CT scanning has entered into the ready armamentarium of parathyroid imaging.

Ultrasound

In experienced hands, ultrasonography is an inexpensive, reproducible and highly sensitive mode of imaging for enlarged parathyroid glands. Its sensitivity is estimated at 75-80% but can range widely as a result of operator dependency. Most experienced endocrine surgeons utilise ultrasound as an adjunct to physical examination, with comparable sensitivities to radiologist-performed exams. During ultrasound, parathyroid glands appear as uniform hypoechoic masses, often in close association but distinct from the thyroid gland. On colour doppler, there is a rim of vascularity (see figure 1).

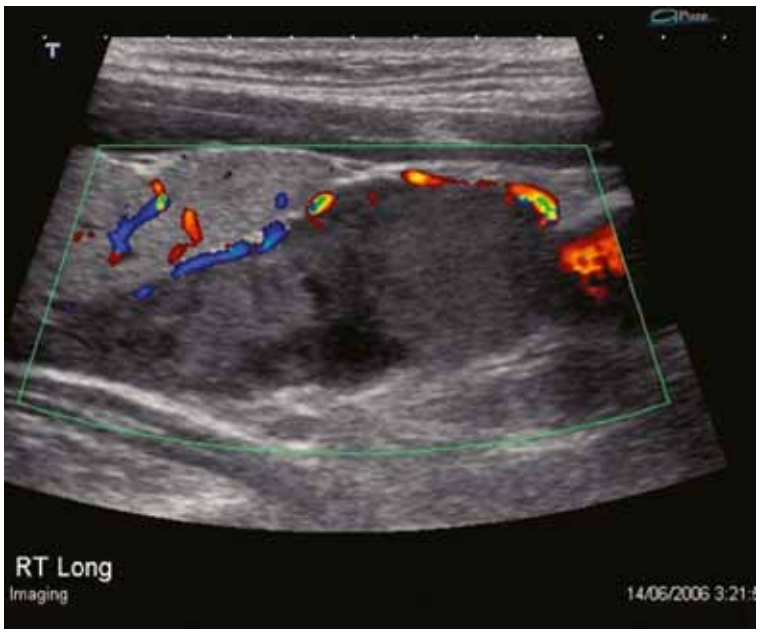
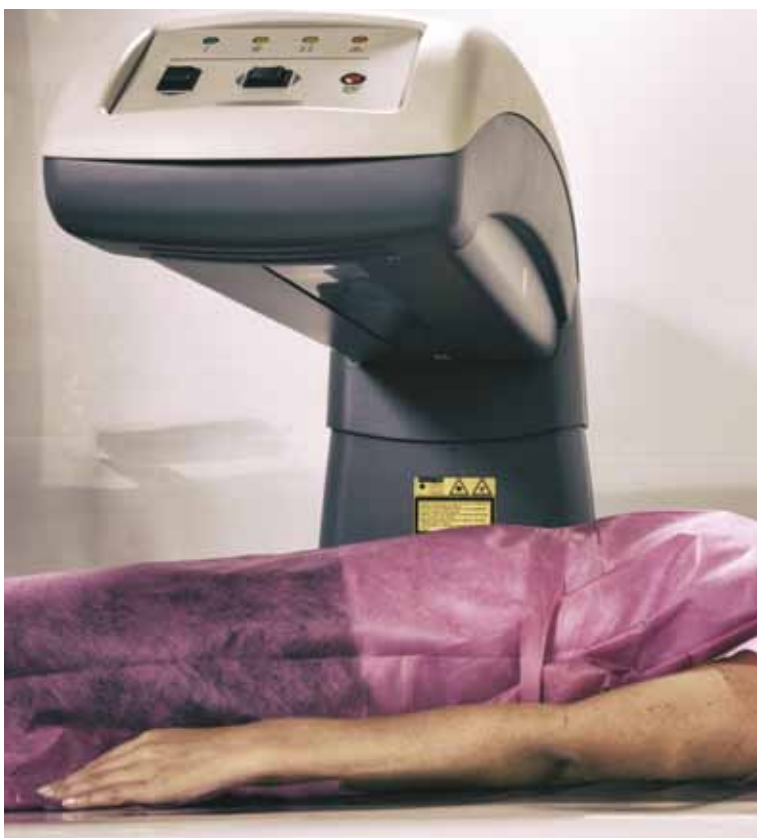


Figure 1: Parathyroid adenoma seen as hypoechoic mass with vascular rim adjacent to thyroid gland and carotid artery. Copyright: Professor Sidhu (author)



Ultrasound further allows the clinician to assess for concomitant thyroid pathology. Worrisome lesions should undergo fine-needle biopsy to exclude thyroid malignancy, which may be addressed in the same operative setting.

The drawbacks of ultrasonography include the inability to image glands below the level of the clavicles, as well as the difficulty of performing the exam in obese patients or patients with smaller adenomas.

Sestamibi scintigraphy

Technetium-labelled sestamibi is rapidly taken up in thyroid and parathyroid tissue. As the mitochondria-rich parathyroid cells retain sestamibi longer than thyroid tissue, delayed images will help identify enlarged parathyroid glands. Scintigraphy should include initial post-injection imaging along with a 2-4-hour delayed scan. To aid in anatomic mapping, pinhole anterior and oblique views should be obtained. Sestamibi scintigraphy may also aid in localisation of ectopically placed adenomas, as demonstrated in figure 2. With the addition of single-photon emission computed tomography (SPECT), the sensitivity of sestamibi scanning is around 80%. In the presence of multiglandular disease, however, the detection rate falls significantly. Concomitant nodular thyroid disease will also increase both the false-positive and false-negative rate of sestamibi scanning.

Computed tomography

Four-dimensional CT scans (4D-CT) exploit the rapid contrast uptake and washout of enlarged parathyroid glands. Its greatest utility is in patients with negative initial imaging, as well as those with persistent or recurrent disease. The sensitivity of 4D-CT in detecting abnormal glands approaches 90%. The anatomic mapping provided by 4D-CT is superior to any other imaging modality, particularly in locations difficult to image by sonography. In figure 3, ultrasound failed to demonstrate a retropharyngeal adenoma, clearly seen on the 4D-CT. Cost, risk of iodinated contrast reaction, and radiation exposure — particularly in younger patients — are the main drawbacks to this mode of localisation.

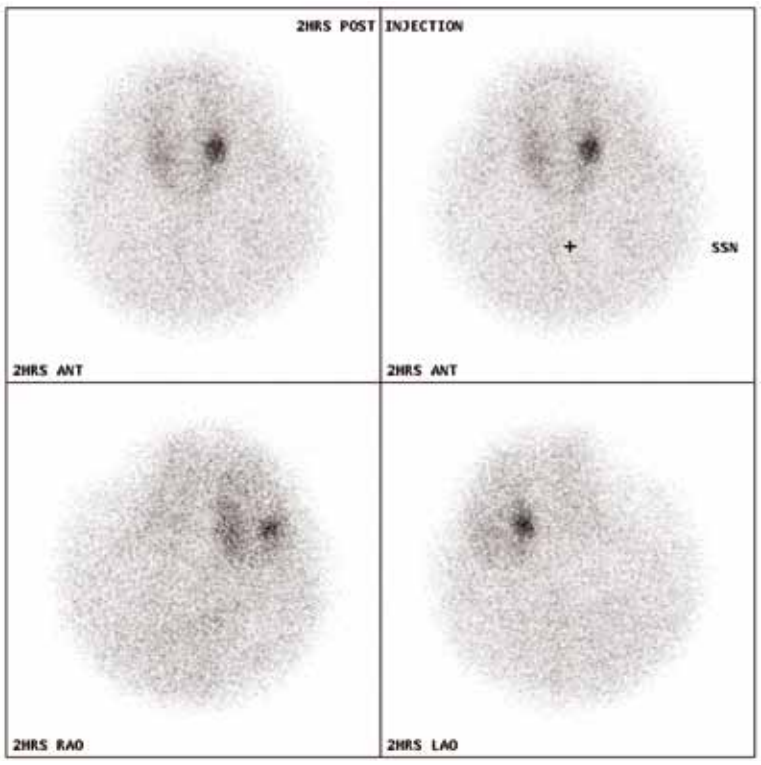


Figure 2: Pinhole views of two-hour delayed scintigraphy of intrathyroidal left parathyroid adenoma (top images demonstrate anterior view; bottom left demonstrates right anterior oblique view; bottom right demonstrates the left anterior oblique view). Copyright: Professor Sidhu (author)

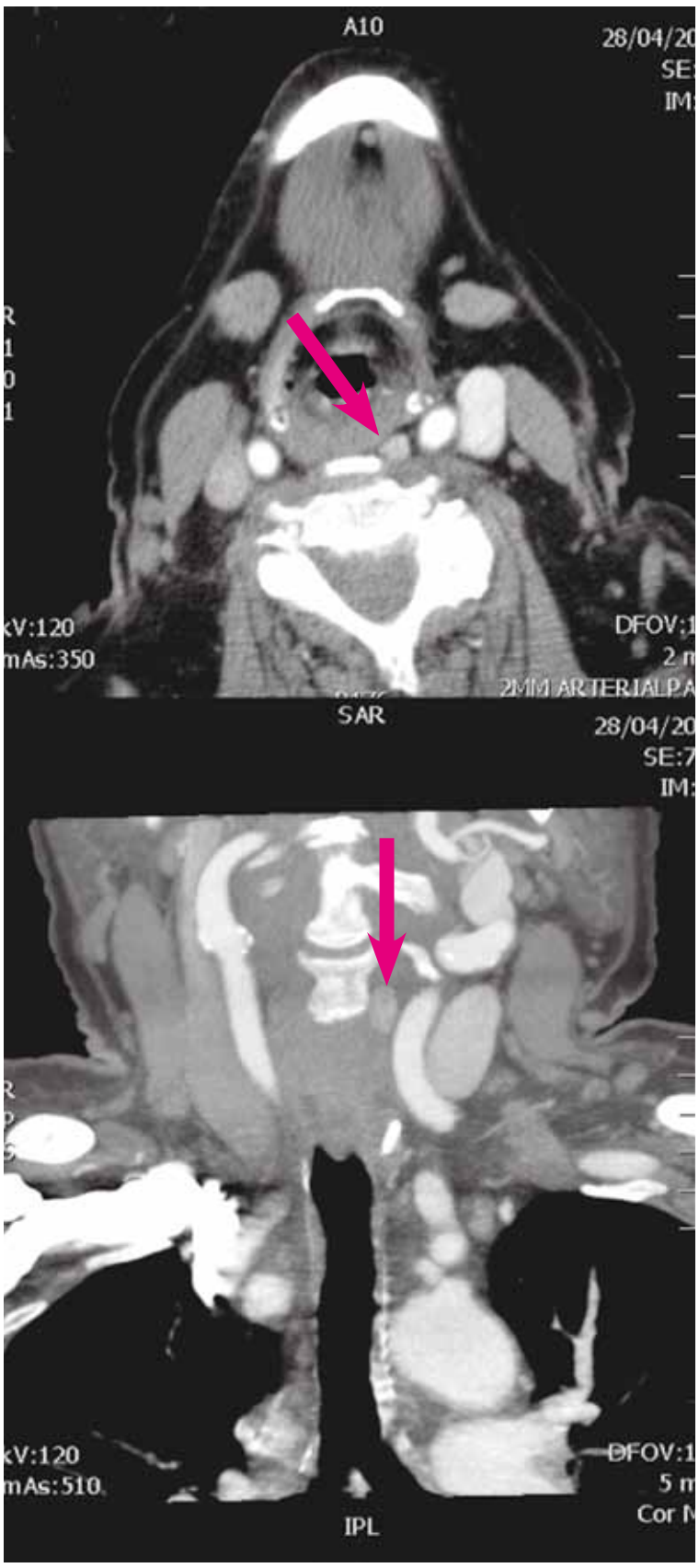


Figure 3: 4D-CT demonstrating undescended retropharyngeal superior left parathyroid adenoma. Copyright: Professor Sidhu (author)

Management

Indications for surgery

DECISION-making in an individual with overt signs and symptoms of primary hyperparathyroidism is straightforward. Surgical excision of abnormal parathyroid gland or glands, undertaken by an experienced parathyroid surgeon, offers cure rates over 98% with minimal risk of serious complications. Thus, surgery is indicated in any patient with symptomatic hypercalcaemia, nephrolithiasis or previous fragility fracture.

However, with the shift in disease profile from obvious symptomatology to subtle or, in some cases, absent findings, the optimal management of patients with asymptomatic primary hyperparathyroidism has been a source of debate. In October 2014, guidelines from the Fourth International Workshop for the Management of Asymptomatic Primary Hyperparathyroidism were published after an exhaustive review of literature by an expert panel.[1] The recommendations for surgical intervention based on serum calcium level, age and target-organ involvement are summarised in table 2. A patient fulfilling any one of the listed criteria should be offered surgery.

In the absence of the above criteria, it is recommended that patients have yearly biochemical assessment of their parathyroid disease. At a minimum, this includes yearly measurement of serum-corrected calcium, creatinine and 24-hour urinary calcium. Skeletal evaluation should be repeated every 1-2 years. If adequate surveillance is not feasible, early surgical intervention is warranted.

Normocalcaemic primary hyperparathyroidism

It is now recognised that normocalcaemic primary hyperparathyroidism is a variant of primary hyperparathyroidism. In these patients, both serum-corrected calcium and ionised calcium are normal with elevated PTH levels. This elevation in circulating PTH is seen in the absence of other known (secondary) causes of elevated PTH (ie, calcium or vitamin D insufficiency, chronic renal failure). Evidence suggests many patients with normocalcaemic primary hyperparathyroidism will eventually progress to become hypercalcaemic or develop signs of target-organ dysfunction. Thus, any patient with this variant should be recommended for surgery in the presence of reduced BMD, vertebral fracture or asymptomatic nephrolithiasis/nephrocalcinosis.

Patients with subtle clinical features

The above recommendations do not include the host of other subtle signs and symptoms that are often noted in patients with primary hyperparathyroidism. The presence of neuropsychiatric symptoms — such as fatigue, weakness, memory loss and depression — as well as cardiovascular disease and gastrointestinal complaints, should be considered for each individual patient. Although these symptoms should not be the sole indication for parathyroid surgery, there exists good evidence that in many individuals, these symptoms are alleviated after surgery. For this reason, any patient with biochemically confirmed primary hyperparathyroidism — even in the absence of the above criteria — would benefit from an informed discussion with an experienced parathyroid surgeon.

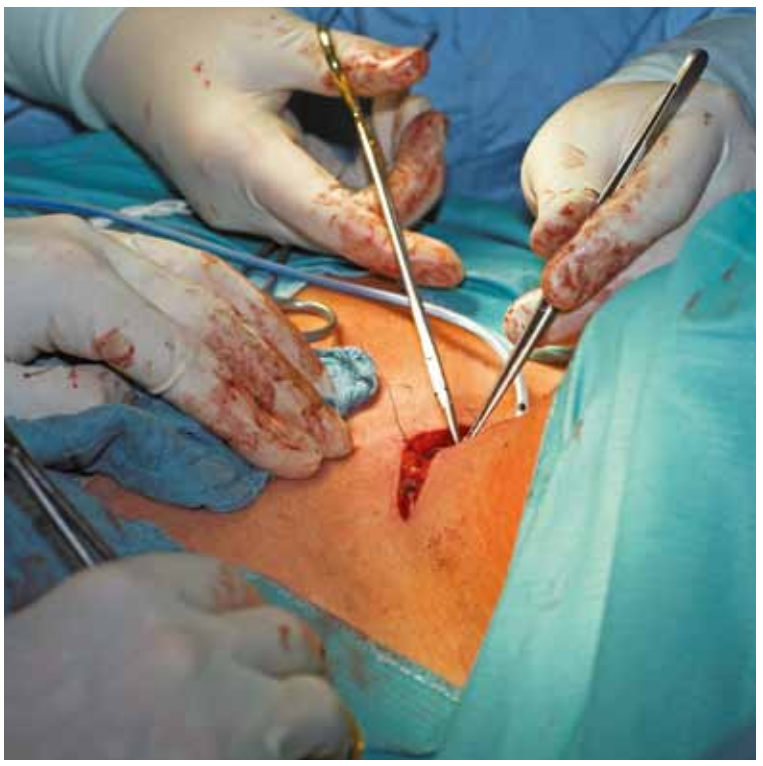


Table 2: Summary guidelines for the surgical management of asymptomatic primary hyperparathyroidism

Age	Under 50
Measured serum calcium	≥0.25mmol/L (1.0mg/dL) above upper limit of normal
Skeletal findings	BMD by DXA: T-score ≤-2.5 at lumbar spine, total hip, femoral neck or distal forearm* Evidence of vertebral fracture by X-ray, CT, MRI or VFA
Renal findings	Creatinine clearance ≤60mL/min 24-hour urine calcium greater than 10mmol/day (400mg/day) Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound or CT

*In premenopausal women, and men below the age of 50, Z-score equal to or less than -2.5 is utilised over the T-score

Surgery is indicated in any patient with symptomatic hypercalcaemia, nephrolithiasis or previous fragility fracture.

Operative approaches

Traditional approach

Traditional parathyroid surgery involves a central neck incision with bilateral cervical exploration, identification of all parathyroid glands and excision of any grossly abnormal or enlarged glands. This procedure, frequently referred to as an 'open parathyroidectomy' or 'four-gland exploration', is most commonly performed under general anaesthesia with an endotracheal tube. Despite recent trends and advances in parathyroid surgery, in the hands of expert surgeons, the four-gland exploration remains an excellent approach, with cure rates approaching 98%.

Major complications, such as injury to the recurrent laryngeal nerve and haematoma, generally occur in 1% of cases or less. Transient hypocalcaemia is relatively common, occurring in upwards of 30% of patients. This is usually a minor complication that may be managed without hospital admission. In patients with elevated preoperative serum alkaline phosphatase levels, however, postoperative hungry bone syndrome may occur, necessitating IV calcium infusion.

Four-gland exploration is the gold-standard approach for patients with known or suspected multiglandular disease or concomitant thyroid pathology. Multiglandular disease is suspected in patients with negative localisation studies, as well as in patients with familial hyperparathyroidism, history of lithium therapy, vitamin D deficiency or mild chronic renal impairment.

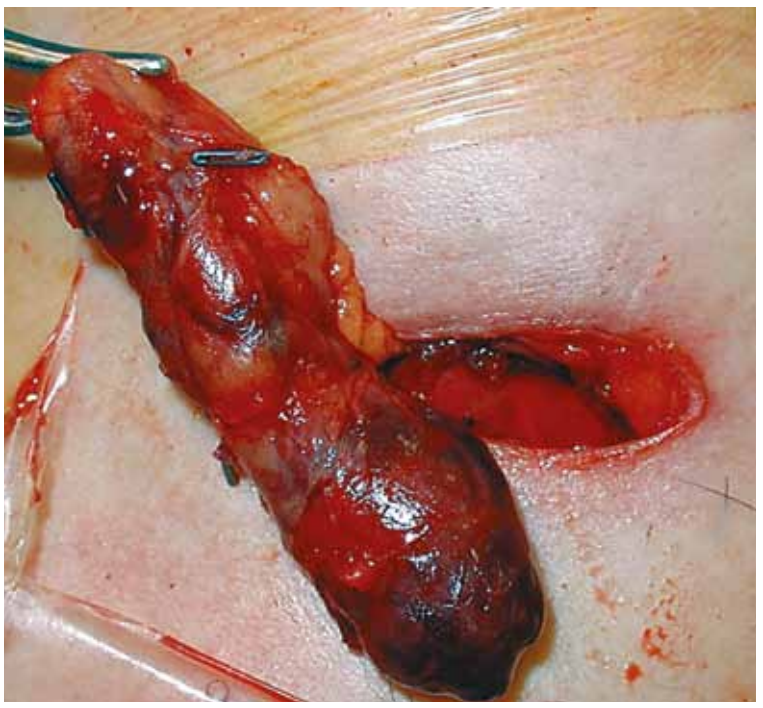


Figure 4: Parathyroid adenoma removed through standard minimally invasive parathyroidectomy incision. Copyright: Professor Sidhu (author)

Minimally invasive approach

As the aetiology of the majority of patients with primary hyperparathyroidism is a single adenomatous gland, focused exploration with identification and excision of that single gland is a viable and acceptable option. Such a procedure can only be performed with adequate localisation. Patients with concordant ultrasound and sestamibi imaging, who do not have a history suggestive of multiglandular disease, can be offered minimally invasive parathyroidectomy. Such procedures, often referred to as focused parathyroidectomy, can be performed through a 2-3cm incision, often placed laterally in the neck (see figure 4). In high-volume units, cure rates and complications are similar to that of the traditional approach, although minimally invasive parathyroidectomy may be associated with less frequent postoperative hypocalcaemia. A focused, unilateral approach has led to an increasing number of procedures being performed on an outpatient basis, reducing the cost associated with overnight hospital admission.

Medical management

In the few patients for whom operative risk is prohibitive, or patients who make an informed decision to decline surgery, medical management may be considered. The goal of such therapy should be to reduce the risk of fragility fractures by improving bone density and lower serum calcium.

Managing fracture risk

A number of pharmacologic agents have been utilised to improve BMD. In postmenopausal women, oestrogen and selective oestrogen receptor modulators (SERMs), such as raloxifene, have been shown to decrease bone resorption. These drugs have not been shown to decrease serum calcium or PTH levels. Further, data showing reduced risk of fragility fractures in primary hyperparathyroidism patients receiving oestrogen or SERM therapy are limited.

The evidence is more convincing for the use of bisphosphonates to increase bone density in patients with primary hyperparathyroidism. Alendronate has been shown to increase bone density at the lumbar spine and hip and is thus recommended for both male and female osteopenic patients with primary hyperparathyroidism for whom surgery is not an option. Alendronate therapy, however, has not yet convincingly been shown to reduce risk of fracture in primary hyperparathyroidism patients; nor is there any effect on serum calcium and PTH levels.

Lowering serum calcium

Cinacalcet is a calcimimetic initially formulated to treat secondary hyperparathyroidism seen in end-stage renal disease, as well as hypercalcaemia associated with parathyroid carcinoma. It works by binding the calcium-sensing receptors in parathyroid cells — thus reducing PTH secretion. Cinacalcet has been shown to be effective in lowering both PTH and calcium levels in patients with primary hyperparathyroidism and is recommended for those in whom surgery is not an option. Its effect on bone density is less well proven, although some data suggest stabilisation of bone loss.

Adverse events have been seen in up to 58% of patients receiving therapy and include arthralgias, myalgias, gastrointestinal symptoms and upper respiratory complaints. Most of these events were of short duration and none were serious or life-threatening.

Cinacalcet is an expensive drug and not recommended for patients with primary hyperparathyroidism amenable to surgical cure. It is currently PBS-subsidised only for those patients suffering from secondary hyperparathyroidism as a result of end-stage kidney disease.

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Prognosis

IN experienced endocrine surgical units, cure rates — defined as normalisation of calcium levels following parathyroid surgery — have been reported to be as high as 98%. Several studies have also demonstrated the improvement of a wide array of clinical manifestations of primary hyperparathyroidism in upwards of 80% of patients. Such manifestations include fatigue, weakness, depression, polyuria, arthralgias and constipation.

Apart from subjective improvement in symptomatology, several studies have demonstrated recovery of target-organ dysfunction following parathyroid surgery.

Skeletal disease

Randomised trials comparing parathyroidectomy with medical therapy have shown that two years following surgery, BMD at the lumbar spine and hip is increased in the surgical group. Although BMD at the spine may remain stable in asymptomatic patients undergoing observation, progressive cortical bone loss (radius and hip) has been noted in asymptomatic patients who are not referred for surgery. Observational studies have also demonstrated the decrease in fracture risk among patients who have had parathyroidectomy.

Renal disease

The benefit of parathyroid surgery for prevention of nephrolithiasis is clearly demonstrated. A 10-year follow-up study involving 121 patients showed all patients with primary hyperparathyroidism who chose not to undergo parathyroidectomy developed nephrolithiasis.[2] In the same study, none of the patients who had undergone surgery developed recurrent stones. Urinary symptoms — such as nocturia, polyuria and haematuria — are also reduced in patients electing to undergo surgery.

Neuropsychiatric disease

There is convincing, albeit inconclusive, evidence demonstrating the benefit of parathyroid surgery for an array of neuropsychiatric

symptoms. The Short Form 36 Health Survey is a health-related quality of life (QOL) questionnaire that has been utilised in a number of studies to assess QOL outcomes following parathyroid surgery. These studies have shown slight improvement in physical and mental health domains after parathyroidectomy. Another QOL questionnaire designed specifically for patients with hyperparathyroidism, the Parathyroid Assessment of Symptoms (PAS) score, was utilised in a multicentric study. Again, modest improvements in neuropsychiatric symptoms were demonstrated following surgery.[3]

Cardiovascular disease

Data demonstrating the benefit of surgery for primary hyperparathyroidism for reducing cardiovascular complications are limited. Recently, however, Scandinavian studies in patients with severe hyperparathyroidism showed increased cardiovascular morbidity and mortality. In these patients, parathyroid surgery offered survival benefit after 15-year follow-up.[4] Other studies looking at specific cardiovascular endpoints failed to demonstrate the benefit of parathyroidectomy in patients with primary hyperparathyroidism. Thus, the presence of cardiovascular disease alone should not be an indication for surgery in patients with mild forms of the condition, as it is likely the cardiovascular complications of primary hyperparathyroidism are not reversed by parathyroidectomy.

Special cases

Familial and syndromic cases

RECENT evidence suggests a far greater genetic predisposition to primary hyperparathyroidism than previously suspected. More than 10% of patients with the condition will harbour a genetic mutation to one of 11 genes implicated in syndromic hyperparathyroidism. Identifying these individuals will help guide clinicians and surgeons in treating both the patients, who are at increased risk of recurrent or persistent disease, as well as at-risk family members. Several of these mutations are associated with the development of endocrine and/or malignant neoplasms, which may need to be addressed prior to parathyroid surgery.

Genetic testing should be considered in select patients in whom a familial history of hypercalcaemia is suspected and with one or more of the following clinical findings: under 45 years of age; presence of multiglandular disease; presence of atypical adenoma or parathyroid carcinoma. Testing should include screening for variants of multiple endocrine neoplasia (MEN 1, MEN 2, MEN 4), familial hypocalciuric hypercalcaemia, and hyperparathyroid–jaw tumour syndrome. A brief review of each of these syndromes is summarised below.

Multiple endocrine neoplasia 1 (MEN 1)

MEN 1 results from a mutation of the tumour-suppressor menin protein. Over 90% of patients will exhibit hyperparathyroidism, usually as a result of four-gland hyperplasia. Thus, the recommended operation for such patients is a subtotal parathyroidectomy in which three-and-a-half glands are removed. In select MEN 1 patients with well-localised, single-gland disease, a focused approach may be acceptable. Associated endocrinopathies are common in MEN 1 and include pituitary adenomas, islet-cell tumours of the pancreas, and carcinoid tumours of the thymus and lung. Patients with familial isolated hyperparathyroidism may also harbour a mutation of the menin gene but lack the associated endocrinopathies seen in MEN 1.

Multiple endocrine neoplasia 2A (MEN 2A)

Mutations of the RET proto-oncogene result in MEN 2. Variations of the mutation yield either the MEN 2A or MEN 3 (MEN 2B) phenotype. Primary hyperparathyroidism is not seen in MEN 3 patients. All patients with MEN 2A develop medullary thyroid carcinoma necessitating total thyroidectomy. At the time of thyroidectomy, only grossly abnormal parathyroid glands need removal, as the risk of recurrent primary hyperparathyroidism is far lower in MEN 2A patients compared with patients with MEN 1. Prior to any planned surgery, however, it is essential to exclude and treat pheochromocytoma, which is frequently encountered in these patients.

Multiple endocrine neoplasia 4 (MEN 4)

Recently, a multiple endocrine neoplasia disorder was discovered in patients initially diagnosed with MEN 1. These patients were unique in that they did not harbour a mutation of the menin protein. Rather, they were found to have mutation of the cyclin-dependent kinase inhibitor, p27. Such mutations left patients vulnerable to MEN 1-like tumours, particularly parathyroid and pituitary adenomas, but also tumours of the pancreas, thyroid, and adrenal gland. Now recognised as MEN 4 syndrome, mutations of the CDNK1-B gene and its phenotypic implications are still being elucidated; thus, no recommendations exist regarding genetic screening and management.

Hyperparathyroid–jaw tumour syndrome (HPT–JT)

This condition results in the mutation of the parafibromin (CDC73) gene. Patients typically present with severe hypercalcaemia as a result of parathyroid carcinoma and may additionally have ossifying jaw fibromas. If known preoperatively, patients with HPT–JT benefit from early, subtotal parathyroidectomy. Intraoperatively, these tumours are exceptionally large, infiltrative and fibrotic. They should be resected en bloc with adjoining muscle and with the ipsilateral thyroid lobe.

Case study

PATRICIA is a 61-year-old woman who presents to her local ED with acute cholecystitis. Her medical history includes several previous admissions for nephrolithiasis — for which she required placement of a ureteral stent and laser lithotripsy six months ago. Upon admission for cholecystitis, she is noted to have a corrected calcium level of 2.84mmol/L. A PTH level is added on to her admission blood work, demonstrating a value of 180pg/mL. Patricia remains in hospital for three days, during which time a laparoscopic cholecystectomy is performed uneventfully. Following discharge, she is referred for evaluation by an experienced endocrine surgeon. Further history reveals a previous right thyroid lobectomy for benign disease. There is no personal history of prior neck irradiation or any family history of nephrolithiasis or endocrine disorders. Physical examination yields a well-healed cervical incision just above the level of the clavicles. There are no palpable remnant thyroid nodules or cervical adenopathy.

Subsequent ultrasound demonstrates a normal left thyroid gland and suggests a parathyroid adenoma in the right superior position. Sestamibi scan shows increased uptake on the right side. To exclude remnant thyroid tissue on the right side, as well as to improve anatomic mapping in a reoperative field, a 4D-CT is performed, which confirms a 2cm right superior parathyroid adenoma just inferior to the cricoid cartilage. Additional testing includes bone mineral densitometry, revealing osteoporosis with T-scores below 2.5 at the spine, hip and distal forearm. Patricia is also noted to be moderately deficient in vitamin D. A preoperative vocal cord assessment confirms full function of both recurrent laryngeal nerves.

Patricia undergoes a focused parathyroidectomy through a small incision within a natural skin crease at the level of the cricoid cartilage. She is noted to have extensive scar tissue from her prior surgery, making the procedure technically challenging. A 2cm adenoma is identified at the predicted location and is able to be safely dissected off the recurrent laryngeal nerve. An intraoperative nerve monitor confirms full function of the nerve at the conclusion of the procedure.

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References

1. Bilezikian JP, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *Journal of Clinical Endocrinology and Metabolism* 2014; 99:3561-69.
2. Silverberg SJ, et al. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *New England Journal of Medicine* 1999; 341:1249.
3. Pasieka JL, et al. Patient-based surgical outcome tool demonstrating alleviation of symptoms following parathyroidectomy in patients with primary hyperparathyroidism. *World Journal of Surgery* 2002; 26:942.
4. Nilsson IL, et al. Clinical presentation of primary hyperparathyroidism in Europe: nationwide cohort analysis on mortality from non-malignant causes. *Journal of Bone and Mineral Research* 2002; 17 Supplement 2:N68.

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Patricia is discharged home the following day with minimal pain and no voice changes. Prior to her discharge, blood tests demonstrate normalisation of her PTH and corrected calcium level. She is commenced on low-dose calcium and vitamin D supplementation for her osteoporosis. On repeat blood testing six months later, her serum calcium level is again in the normal range. Two years later, Patricia is noted to have no further episodes of nephrolithiasis and improving BMD.

Conclusion

IN the developed world, primary hyperparathyroidism has now become a silent disease, with the vast majority of patients presenting without the overt signs and symptoms that once made the condition easily identifiable. Its diagnosis is entirely biochemical, characterised by hypercalcaemia in the presence of elevated or inappropriately normal PTH. Parathyroid imaging is frequently not diagnostic. This misconception is a common reason for treatment delay, resulting in potentially avoidable complications of renal and bone disease. Once identified, detailed questioning and investigation will prove that many of these patients are subtly symptomatic and thus would benefit from definitive surgical cure in the hands of an experienced parathyroid surgeon. In the absence of symptoms, easy-to-follow guidelines have been made available by an international consensus. Future research will better identify the optimal treatment of those patients who are truly asymptomatic.

Summary

Primary hyperparathyroidism results from an overproduction of parathyroid hormone in the absence of secondary modulators of PTH production.

In 85% of cases, overproduction of PTH arises from a single adenomatous gland. Multiglandular disease accounts for the remaining 15% of cases.

Primary hyperparathyroidism affects on average 25-60 individuals per 100,000. This figure rises sharply in the female and elderly population.

Primary hyperparathyroidism primarily targets the skeletal and urinary system; however, neuropsychiatric and cardiovascular health may also be affected.

Diagnosis is confirmed with the finding of elevated serum calcium levels and elevated or non-suppressed levels of PTH.

Normocalcaemic primary hyperparathyroidism is a known variant of the disease and should be considered in patients with evidence of target-organ dysfunction.

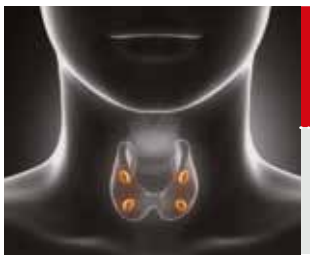
Localisation studies are not necessary for the establishment of diagnosis.

Ultrasound and sestamibi imaging aid in localising abnormal glands. In the event of discordant imaging, 4D-CT scans can be utilised.

Well-established guidelines exist in managing asymptomatic patients with primary hyperparathyroidism.

Familial syndromes are more common than previously believed and should be carefully investigated.

In the hands of experienced parathyroid surgeons, operative intervention for primary hyperparathyroidism is a safe, effective and lasting cure for the disease.



How to Treat Quiz

Primary hyperparathyroidism — 20 February 2015

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points.
We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

GO ONLINE TO COMPLETE THE QUIZ

www.australiandoctor.com.au/education/how-to-treat

1. Which TWO statements regarding the epidemiology and aetiology of primary hyperparathyroidism are correct?

a) Primary hyperparathyroidism is the most common cause of hypercalcaemia in the non-hospitalised patient.
b) The incidence of primary hyperparathyroidism decreases with age, with males more commonly affected than females.
c) Severe bone loss, nephrocalcinosis, gout and pseudogout are rare manifestations of symptomatic primary hyperparathyroidism in the developed world.
d) Twenty per cent of patients with primary hyperparathyroidism are asymptomatic.

2. Which THREE differential diagnoses should be considered in a patient with hypercalcaemia?

a) Malignancy.
b) Diabetes.
c) Chronic granulomatous disease.
d) Excessive dietary intake.

3. Which THREE medications can affect calcium homeostasis or parathyroid hormone (PTH) secretion to cause hypercalcaemia?

a) Antacids.
b) Thiazide diuretics.
c) SSRIs.
d) Lithium.

4. Which TWO statements regarding pathology tests to investigate primary hyperparathyroidism are correct?

a) Ten per cent of circulating calcium is bound to albumin, meaning serum albumin should be requested when assessing calcium concentrations.
b) Vitamin D levels should be assessed because deficiency can accelerate the end-organ effects of primary hyperparathyroidism.
c) Phosphate, alkaline phosphatase, urea and creatinine should be assessed in patients with suspected primary hyperparathyroidism to assess for end-organ effects.
d) Assessment of eGFR is sufficient to assess the degree of renal insufficiency in primary hyperparathyroidism.

5. Which TWO statements regarding imaging to investigate primary hyperparathyroidism are correct?

a) Only patients with symptomatic disease need abdominal imaging for end-organ effects.
b) Assessing bone mass density (BMD) at the distal radius is especially important in primary hyperparathyroidism because parathyroid hormone predominantly affects cortical bone.
c) Ultrasound has a sensitivity of up to 80% for identifying enlarged parathyroid glands.
d) All patients with primary hyperparathyroidism should have four-dimensional CT scanning (4D-CT), as the test is highly sensitive for parathyroid abnormalities.

6. Which THREE features indicate surgery is warranted in a patient with primary hyperparathyroidism?

a) Age under 50.
b) Evidence of vertebral fracture on imaging.
c) Presence of nephrolithiasis or nephrocalcinosis on imaging.
d) Confirmed adenoma on parathyroid imaging.

7. Which TWO statements regarding the operative approaches to parathyroid surgery for primary hyperparathyroidism are correct?

a) The traditional four-gland exploration approach achieves a near 98% cure rate when performed by an expert surgeon.
b) Recurrent laryngeal nerve injury is a common complication of four-gland exploration surgery, occurring in about 20% of cases.
c) Transient hypocalcaemia is an uncommon complication of traditional parathyroid surgery, occurring in under 5% of cases.
d) Focused exploration and excision of a single gland may be undertaken in patients with confirmed single adenomatous gland involvement.

8. Which TWO statements regarding the medical management of primary hyperparathyroidism are correct?

a) In postmenopausal women, selective oestrogen receptor modulators (SERMs) decrease serum calcium and parathyroid hormone levels and have a well-established role in preventing fragility fractures.
b) The bisphosphonate alendronate increases bone density at the lumbar spine and hip and is recommended for osteopenic males and females who are not surgical candidates.
c) Cinacalcet, a calcimimetic that lowers both parathyroid hormone and calcium levels, is only recommended for patients with primary hyperparathyroidism who are not surgical candidates.
d) Adverse events with cinacalcet may include arthralgia, myalgia, gastrointestinal and respiratory symptoms, but these are rare, occurring in about 1% of patients.

9. Which TWO statements regarding prognosis following treatment for primary hyperparathyroidism are correct?

a) There is no difference in fracture risk in patients who have undergone parathyroidectomy compared with those who have been medically managed for primary hyperparathyroidism.
b) Parathyroid surgery prevents nephrolithiasis and reduces urinary symptoms in patients with primary hyperparathyroidism.
c) There is no evidence of any benefit to neuropsychiatric symptoms with parathyroid surgery for primary hyperparathyroidism.
d) Cardiovascular complications of primary hyperparathyroidism are not reversed by parathyroidectomy, so in mild cases, the presence of cardiovascular disease alone should not be considered an indication for surgery.

10. Which TWO statements regarding familial and syndromic causes of primary hyperparathyroidism are correct?

a) Fewer than 1% of patients with primary hyperparathyroidism will harbour an identifiable genetic cause of the condition.
b) Hyperparathyroidism affects only 10% of patients with MEN 1, in whom the cause is usually a single gland adenoma.
c) Patients with primary hyperparathyroidism due to MEN 1 have an increased risk of other tumours, including tumours of the pancreas and thymus.
d) Hyperparathyroid–jaw tumour syndrome (HPT–JT) causes large, infiltrative and fibrotic parathyroid carcinomas, as well as ossifying jaw fibromas.

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2014-16 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

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NEXT WEEK

Antenatal visits are part of pregnancy care and common in general practice. They are a chance to provide social and lifestyle advice when women are often receptive. This How to Treat reviews the principles of routine preconception and antenatal care. The authors are **Dr Jennie Connell**, fellow in maternal fetal medicine, Gold Coast University Hospital, Queensland; and **Professor David Ellwood**, professor of obstetrics and gynaecology, Griffith University, Queensland, and director of maternal fetal medicine, Gold Coast University Hospital, Queensland.