Hyperparathyroidism is due to increased activity of the parathyroid glands, either from an intrinsic abnormal change altering excretion of parathyroid hormone (primary or tertiary hyperparathyroidism) or from an extrinsic abnormal change affecting calcium homeostasis stimulating production of parathyroid hormone (secondary hyperparathyroidism). Primary hyperparathyroidism is the third most common endocrine disorder, with the highest incidence in postmenopausal women. Asymptomatic disease is common, and severe disease with renal stones and metabolic bone disease arises less frequently now than it did 20–30 years ago. Primary hyperparathyroidism can be cured by surgical removal of an adenoma, increasingly by minimally invasive parathyroidectomy. Medical management of mild disease is possible with bisphosphonates, hormone replacement therapy, and calcimimetics. Vitamin D deficiency is a common cause of secondary hyperparathyroidism, particularly in elderly people. However, the biochemical definition of vitamin D deficiency and its treatment are subject to much debate. Secondary hyperparathyroidism as the result of chronic kidney disease is important in the genesis of renal bone disease, and several new treatments could help achieve the guidelines set out by the kidney disease outcomes quality initiative.

**Introduction**

Ionised calcium in plasma is closely regulated and ranges from 1.1 mmol/L to 1.3 mmol/L (calcium adjusted for albumin 2.2–2.6 mmol/L). Precise control of ionised calcium is needed to ensure optimum function of physiological processes, particularly cell signalling, neural function, muscular function, and bone metabolism. Pivotal regulation of ionised calcium is secretion of parathyroid hormone from the parathyroid glands, usually located in the neck, which respond to changes in circulating ionised calcium via the calcium-sensing receptor (CaSR) located on the surface of the chief cells. Parathyroid hormone has a major biological function in maintaining ionised calcium and phosphate within the reference range by stimulating specific receptor-mediated responses in cells throughout the body. If a decrease in circulating ionised calcium occurs, parathyroid hormone increases and has three major functions that help to restore a normal circulating concentration (figure 1): receptor-mediated tubular reabsorption of calcium (kidney); stimulation of osteoclast resorption to release skeletal calcium (bone); and increasing activity of renal 1 hydroxylase, resulting in production of 1,25-dihydroxyvitamin D and increasing calcium absorption (bowel). The increase in calcium in response to these effects mediated by parathyroid hormone acts via a classic endocrine feedback loop on the CaSR, decreasing secretion of parathyroid hormone.

Components in this regulatory system can cause excessive secretion of parathyroid hormone and hyperparathyroidism. Primary hyperparathyroidism can occur when one or more parathyroid glands secrete excess parathyroid hormone, resulting in hypercalcaemia (intrinsic abnormal change). Single gland adenoma is the most common cause (75–85%), multigland adenoma arises in a substantial proportion (two glands in 2–12% of cases, three glands in <1–2%, and four or more in <1–15%), and parathyroid carcinoma is rare (~1%). Lower pole adenomas (in relation to the thyroid) are more common than are upper pole adenomas; sizes range from 1 cm to 3 cm and weights from 0.3 g to 4.5 g. Ectopic glands may be present (4–16% of cases), indicating embryology and parathyroid tissue might be within the mediastinum (often associated with the thymus), around the

**Primary hyperparathyroidism**

**Definition, pathology, cause, and epidemiology**

In primary hyperparathyroidism, in the absence of a known or recognised stimulus, one or more of the four parathyroid glands secrete excess parathyroid hormone, resulting in hypercalcaemia (intrinsic abnormal change). Single gland adenoma is the most common cause (75–85%), multim gland adenoma arises in a substantial proportion (two glands in 2–12% of cases, three glands in <1–2%, and four or more in <1–15%), and parathyroid carcinoma is rare (~1%). Lower pole adenomas (in relation to the thyroid) are more common than are upper pole adenomas; sizes range from 1 cm to 3 cm and weights from 0.3 g to 4.5 g. Ectopic glands may be present (4–16% of cases), indicating embryology and parathyroid tissue might be within the mediastinum (often associated with the thymus), around the...

**Search strategy and selection criteria**

The following terms were used to search PubMed, Medline, and the Web of Science for pertinent articles:

“hyperparathyroidism”, “primary hyperparathyroidism”, “secondary hyperparathyroidism”, “tertiary hyperparathyroidism”, “chronic kidney disease”, “vitamin D deficiency”, and “familial benign hypercalcaemic hypocalciuria”. There was no restriction on language, and all years were searched. A computer link program was used to exclude duplicate articles, and linked articles were searched for any missing publications of note. Additionally, a personal collection of pertinent articles made by the author over the past 20 years were used to identify important information related to the review.
absorption; and an effect on osteoclasts to increase resorption releasing calcium from bone.  
stimulate the synthesis of 1,25-dihydroxyvitamin D in the kidneys, which acts on the gut to promote calcium absorption, and an effect on osteoclasts to increase resorption releasing calcium from bone.

Figure 1: Parathyroid hormone response to decreased ionised calcium
In response to a decrease in ionised calcium detected at the calcium-sensing receptor, synthesis and secretion of parathyroid hormone increases and has three major effects: to increase calcium reabsorption at the kidney; to stimulate the synthesis of 1,25-dihydroxyvitamin D in the kidneys, which acts on the gut to promote calcium absorption; and an effect on osteoclasts to increase resorption releasing calcium from bone.

Table 1: Changing clinical presentation of primary hyperparathyroidism

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrolithiasis</td>
<td>51–57%</td>
<td>17–37%</td>
</tr>
<tr>
<td>Hypercalcinia</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>Overt skeletal disease</td>
<td>10–23%</td>
<td>1–4–14%</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0 6–18%</td>
<td>22–80%</td>
</tr>
</tbody>
</table>

Modified from reference 12.

Diagnosis
70–80% of patients with primary hyperparathyroidism have no obvious symptoms or signs of disease, with their disease detected by an incidental finding of hypercalcaemia. Table 1 shows the changing clinical presentation.12 Symptoms and clinical signs often relate to chronic hypercalcaemia rather than to increased parathyroid hormone.13,14 In the 20–30% of symptomatic patients, nephrolithiasis is the most common symptom. Overt skeletal disease is rare, but osteoporosis with related fracture is increasing.15 Acute hypercalcaemic crisis with nephrogenic diabetes insipidus and dehydration is most likely in patients with a concentration of albumin-adjusted calcium greater than 3·0 mmol/L. Acute pancreatitis is an uncommon but serious complication. Clinically evident neuromuscular disease is uncommon, but proximal muscle weakness due to type II muscle fibre atrophy can be seen in association with severe bone disease (osteitis fibrosa cystica). Psychiatric symptoms include depression, dementia, confusion, and stupor. Associations have been described with hypertension, diabetes, gastrointestinal ulceration, gout, increased weight, and hyperlipidaemia.

Primary hyperparathyroidism is the most common cause of hypercalcaemia in many surveys, and figure 2 outlines an initial approach to the differential diagnosis. Measurement of intact parathyroid hormone (1–84) has resulted in a substantial improvement in the diagnostic discrimination of the causes of hypercalcaemia. Intact parathyroid hormone assays also measure a parathyroid hormone (7–84) fragment;16 however, a whole parathyroid hormone assay has been developed that does not detect this fragment.17 The percentage of parathyroid hormone (7–84) within each patient sample remains fairly constant, although increasing in chronic kidney disease,18 and so intelligent application of such assays (figure 2) is advisable. Some patients with primary hyperparathyroidism have a parathyroid hormone (1–84) within the reference range, which is inappropriate for the prevailing hypercalcaemia. Initial assessment suggested most patients with this
disease have a whole parathyroid hormone concentration above the reference range; however, a comparative study of two intact assays and a whole parathyroid hormone assay confirmed a high correlation between the methods. Moreover, a further comparison did not show an improvement in diagnostic sensitivity of the whole parathyroid hormone assay.

An important differential diagnosis in patients with hypercalcaemia with concentration of parathyroid hormone modestly increased or within the reference range is familial benign hypocalciuric hypercalcaemia, which is often diagnosed after an unsuccessful parathyroidectomy. 9% of consecutive patients referred to the US National Institutes of Health (NIH) having had a failed parathyroidectomy had familial benign hypocalciuric hypercalcaemia. A family screening study estimated the prevalence to be between one in 15 625 and one in 31 250. Specific questions have to be asked regarding a family history of hypercalcaemia and failed neck surgery when this disease is a possibility. Classic symptoms and signs of primary hyperparathyroidism are rare in familial benign hypocalciuric hypercalcaemia, with prevalence of renal stones less than 1% and minimal skeletal pathological changes. An increased incidence of relapsing pancreatitis is reported, but alcohol misuse and biliary disease are possible confounders. Familial benign hypocalciuric hypercalcaemia is autosomal, dominant, and has lifelong penetrance for hypercalcaemia, with hypocalciuria near 100%. Most patients have a loss of function mutation of the CaSR gene on chromosome 3. Several mutations in CaSR exist, some outside the coding region of the receptor. As a result of the CaSR defects, inappropriate secretion of parathyroid hormone occurs at increased concentrations of albumin-adjusted calcium, with reduced responsiveness to changes in plasma calcium and a shift in the calcium-parathyroid hormone set-point. Increased renal tubular reabsorption of calcium persists even after total parathyroidectomy. Several factors can assist in the diagnosis (table 2). A calcium creatinine clearance ratio of less than 0.01 is suggested as the cut-off separating familial benign hypocalciuric hypercalcaemia from primary hyperparathyroidism (sensitivity 85%, specificity 88%, positive predictive value 85%). Gunn and Gaffney have reviewed biochemical tests differentiating both these diseases.

Treatment
The only cure for primary hyperparathyroidism is surgical removal of a parathyroid adenoma or adenomas. Experienced surgeons are estimated to identify an affected gland in 95% of cases. The standard operation is a full neck exploration with identification of all glands, recognising that 15–25% can have multiple adenomas. Local anaesthesia and minimally invasive parathyroidectomy are increasingly used. The value of minimally invasive parathyroidectomy is debated, but it can have advantages in an elderly population who are at risk from a general anaesthetic and full neck exploration.

Minimally invasive parathyroidectomy requires pre-operative localisation studies with identification of one adenoma, and might benefit from intraoperative determination of parathyroid hormone confirming adenoma removal. Localisation techniques include ultrasound, MRI, and computerised axial tomography, with the greatest reported success with use of technetium-labelled sestamibi-single photon emission CT. Up to 89% of single parathyroid adenomas can be localised by this method. Imaging techniques are less successful for investigation of patients with mild hypercalcaemia and in identification of multiple glands.

Parathyroid hormone assays with short incubation times have established intraoperative measurements of this hormone as a method to determine successful removal of an adenoma, which can affect intraoperative decisions when localisation techniques are equivocal. A 50% decrease in parathyroid hormone from baseline 5–10 min after excision of an adenoma is evidence of successful parathyroidectomy. A delay of at least 30 min after excision can improve sensitivity. Debate about the

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**Figure 2:** Initial investigation of hypercalcaemia
Biochemical investigation of hypercalcaemia should result in measurement of parathyroid hormone (1–84) on a sample taken before any medical intervention, with the initial classification into parathyroid or non-parathyroid causes on the basis of the combination of concentrations of parathyroid hormone and calcium. Further complex tests might be needed to establish the precise cause of hypercalcaemia in some patients. Intact parathyroid hormone (1–84) measured with Nichols Institute diagnostic method. Ca/Cr = calcium creatinine clearance ratio.

FBHH=familial benign hypocalciuric hypercalcaemia.
value of intraoperative parathyroid hormone and the role of minimally invasive parathyroidectomy continues, with some supporting this technique but others maintaining that a bilateral approach offers the best opportunity for long-term cure. Panel 1: Recommendations for surgery from the National Institutes of Health consensus conference on primary hyperparathyroidism in 1990 and 2002

- Serum albumin-adjusted calcium greater than 0.25 mmol/L above the upper limit of local laboratory reference range
- Urine calcium greater than 10 mmol per 24 h
- Creatinine clearance reduced by 30% or more
- Bone mineral density T score less than –2.5 (at any site)
- Age younger than 50 years
- Patient request; adequate follow-up unlikely

Guidelines for surgery

The present clinical profile of primary hyperparathyroidism is of a fairly mild asymptomatic disease in most patients. Although surgery is recommended for most symptomatic patients, a large subgroup exists who are asymptomatic and might not benefit from surgery. A consensus development panel produced guidelines in 1990, which were updated in 2002 and are under review, giving specific indications for when surgery is recommended (panel 1). However, high-quality evidence for many of these recommendations is not available. With recognition that in a few patients there is disease progression, recommendations exist regarding follow-up that could be undertaken in primary or secondary care. Changes that meet the criteria for surgery need to be assessed in view of the prevailing clinical disorder, but increasing experience and confidence with minimally invasive parathyroidectomy is likely to affect such decisions in future.

A review in the USA showed a large divergence in surgical practice and widespread failure to apply the NIH guidelines. This finding was affected by experienced surgeons who are very willing to operate on several asymptomatic or minimally symptomatic patients. However, a small but not insignificant mortality and morbidity is associated with surgical procedures, which increases with patient age; therefore outcome data should be reviewed after parathyroidectomy. After successful parathyroidectomy, plasma, albumin-adjusted calcium, parathyroid hormone, phosphate, and calcium in the urine all quickly return to normal. Indicators of bone resorption normalise quicker than formation. Furthermore, osteoblast is greater than osteoclast activity, resulting in a substantial improvement in bone mineral density. Bone mineral density in the hip and spine show the greatest increase, as do patients with osteoporosis or osteopenia before surgery.

A crucial question in primary hyperparathyroidism is whether surgery decreases the risk of future fracture. Cohort studies suggest patients with this disease have a substantial increased risk of vertebral, distal forearm, rib, and all fractures compared with a population matched for age and sex. Although most reports confirm increased risk of forearm fracture and vertebral fracture, others did not find such a difference. The relative risk of fracture decreased after surgery in some studies, and a retrospective cohort study of 1569 patients (452 of whom had had a parathyroidectomy) reported a significant increase in 10-year fracture-free survival, mainly hip fractures, after parathyroidectomy (59% vs 73%). Between 400 and 900 patients would need to be followed up prospectively for several years to provide information about whether vertebral fracture risk increases in patients with primary hyperparathyroidism.

Renal stone disease shows a variable response to surgery. Parfitt and colleagues reported a 90% reduction in incidence, but others have shown a 30–50% risk of recurrence 3–5 years after parathyroidectomy. Continued stone formation is considered attributable to non-parathyroid causes. In one study, patients with primary hyperparathyroidism had a significant increased risk of stone formation 10 years before surgery that gradually decreased but remained high, compared with controls, up to 10 years after surgery. Younger age, preoperative stones, stricture of the ureter, and higher urine calcium are all serious risk factors for stones after surgery.

Hypertension and cardiac abnormal changes are reasons to undertake parathyroidectomy, but published

<table>
<thead>
<tr>
<th>FBHH</th>
<th>Primary HPT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Unrelated to calcium</td>
</tr>
<tr>
<td><strong>Plasma albumin-adjusted calcium (mmol/L)</strong></td>
<td>2.55–3.5</td>
</tr>
<tr>
<td><strong>Intact parathyroid hormone (pg/mL)</strong></td>
<td>Most within reference range (0.9–11.0; median 3.0)</td>
</tr>
<tr>
<td><strong>Plasma magnesium (mmol/L)</strong></td>
<td>Trend higher (0.78–1.18; median 0.94)</td>
</tr>
<tr>
<td><strong>Plasma 1,25-dihydroxyvitamin D (pg/mL)</strong></td>
<td>Within reference range (54–134; median 87)</td>
</tr>
<tr>
<td><strong>Ca/Cr</strong></td>
<td>Most &lt;0.01 (0.001–0.018; median 0.005)</td>
</tr>
</tbody>
</table>

Ca/Cr = calcium creatinine clearance ratio. Table modified from reference 23.

Table 2: Comparison of clinical and biochemical findings in familial benign hypocalciuric hypercalcaemia (FBHH) and primary hyperparathyroidism (HPT)
work suggests long-term control of hypertension is not improved by surgery.\(^{54,55}\) Left ventricular hypertrophy decreases after surgery in some patients,\(^{56,57}\) and parathyroidectomy can slow the progression of aortic and mitral valve calcification.\(^{38}\)

Neurological and neuropsychiatric symptoms are especially difficult to define and investigate. Most studies of symptoms such as fatigue, weakness, lassitude, anxiety, and depression do not find objective evidence of significant changes after parathyroidectomy and can be complicated by the absence of suitable controls.\(^{51,52}\) In a randomised study of surgery in 53 patients with mild primary hyperparathyroidism,\(^{53}\) the short form-36 (SF-36) health survey assessed changes every 6 months for 2 years. In two of nine domains, social and emotional role functioning, patients who did not receive operative intervention significantly declined in these areas of functioning. However, the absence of blinding, an unclear randomisation schedule, and a weakness in statistical analysis have been cited as problems with this trial.\(^{62}\) In an uncontrolled open prospective study of 74 patients, a significant improvement in SF-36 scores was noted 1 year after parathyroidectomy in five (asymptomatic) and seven (symptomatic) of eight domains of the SF-36 health survey.\(^{53}\) In another uncontrolled study of 100 patients, all eight domains of the SF-36 (version 2) score significantly improved, for up to 1 year, irrespective of whether the patients met the NIH operative criteria.\(^{64}\)

A review has drawn attention to difficulties in this area of management for primary hyperparathyroidism.\(^{51}\) Few controlled studies exist. In one study that used thyroidectomy as a comparator, patients assigned to thyroidectomy reported no benefit from surgery; however, patients with primary hyperparathyroidism were older and had more symptoms, and significant institutional differences existed between study sites.\(^{51}\) In other studies using thyroidectomy as a control, although significant improvement in psychiatric and neurocognitive testing was noted in patients with primary hyperparathyroidism, the possibility of a significant placebo effect of surgery was raised.\(^{65,66}\) A prospective study of 191 patients with mild asymptomatic primary hyperparathyroidism who were randomised to medical observation or surgical intervention has not shown any benefit of operative treatment on SF-36 or psychological symptoms after 2 years.\(^{67,68}\)

**Acute management of hypercalcaemia**

Management of hypercalcaemia (crisis or deterioration in clinical status) initially involves rehydration with intravenous 0·9% NaCl. Most patients will be fluid depleted and can require 2–4 L of fluid within the first 24 h. Provision of NaCl will restore normovolaemia, decrease uraemia, and promote calcium excretion in the urine. In the subsequent 24–48 h, a further 2–3 L of NaCl might be needed. If a patient is being treated so that they are fit to undergo surgery within a few days, then intravenous bisphosphonates should be avoided since their use can result in significant problems related to hypocalcaemia after parathyroidectomy. Calcitonin in the dose of 200 IU every 8 h might be helpful in decreasing albumin-adjusted calcium, and there is good evidence that cinacalcet can also be of value in the short term (doses of 30–50 mg twice per day) to maintain a reduction of albumin-adjusted calcium.

**Medical treatment**

Several patients will not meet the criteria for surgery, and many are not willing to have, or are unsuitable for, an operation. Which patients will deteriorate and show progression of their disease is impossible to predict. For these patients, medical treatments should be considered.

Since a high percentage of patients are postmenopausal women, treatment targeting improvement in bone mineral density and calcium homoeostasis is an attractive alternative to surgery. Hormone replacement therapy in primary hyperparathyroidism is associated with a significant reduction in albumin-adjusted calcium (0·1–0·3 mmol/L).\(^{69,70}\) Antagonism of bone resorption mediated by parathyroid hormone is associated with improvement in bone mineral density at the lumbar spine and femoral neck. During 4 years, hormone replacement therapy results in a 4–8% increase in bone mineral density at trabecular and cortical sites.\(^{71}\) No change is recorded in plasma parathyroid hormone or phosphate. The Women's Health Initiative study\(^{72}\) raised concerns about hormone replacement therapy, changing prescribing habits and resulting in many women now being reluctant to take this treatment. Raloxifene—a selective oestrogen receptor modulator—has the beneficial oestrogen-agonist effects on bone and lipid metabolism, with antagonist effects on the breast and uterus. In a few patients, raloxifene 60 mg or 120 mg per day decreased albumin-adjusted calcium and lowered indicators of resorption and formation, while leaving parathyroid hormone unaffected.\(^{73,74}\) A modest increase in bone mineral density was noted after 1 year of treatment with these doses of raloxifene.

Etidronate is fairly ineffective in primary hyperparathyroidism.\(^{75}\) Clodronate temporarily reduces albumin-adjusted calcium (for 3 months) and reduces bone resorption, but hypercalcaemia and hypercalciuria return on stopping treatment.\(^{76}\) Intravenous pamidronate causes an acute transient decrease in calcium adjusted for albumin, urine calcium, and bone turnover indicators; however, an increase in parathyroid hormone and 1,25-dihydroxyvitamin D occurs, which can restrict effectiveness.\(^{77}\) Improved functional independence measure is seen in elderly patients after intravenous pamidronate.\(^{78}\) The medical treatment showing the greatest promise in primary hyperparathyroidism is oral alendronate. In four trials including 119 postmenopausal women and 24 men
treated for up to 2 years, the investigators reported a significant increase in lumbar spine and femoral neck bone mineral density, with no substantial change in radial bone mineral density. With alendronate 10 mg per day, a transient decrease in albumin-adjusted calcium was noted, but no long-term effect, and parathyroid hormone and bone turnover indicators decreased significantly. A randomised double-blind, placebo-controlled crossover trial of alendronate 10 mg per day in 44 patients with asymptomatic primary hyperparathyroidism confirmed the significant effect on lumbar spine and total hip bone mineral density, and no effect was noted on radial bone mineral density after 12 or 24 months of treatment. Bone turnover indicators decreased significantly, but serum calcium, parathyroid hormone, and urine calcium did not differ between groups. Combining the results of studies suggests that bisphosphonates in general and alendronate in particular might be useful in the treatment of this disease when parathyroidectomy is not recommended or is not possible.

The CaSR has become a target for therapeutic manipulation, and calcimimetics have been developed that decrease secretion of parathyroid hormone. They bind to the CaSR and increase its sensitivity to extracellular calcium. Cinacalcet is an orally active calcimimetic that is used to treat secondary hyperparathyroidism in chronic kidney disease. In a 1-year treatment trial, patients with primary disease were initiated over 12 weeks on increasing doses of cinacalcet (30–50 mg twice per day) or placebo. 73% of patients receiving this drug normalised concentrations of albumin-adjusted calcium compared with 5% receiving placebo. Parathyroid hormone decreased by 7.6% whereas the placebo group increased by 7.7%. Three patients receiving cinacalcet developed asymptomatic hypocalcaemia and two were symptomatic. Despite significant decreases in parathyroid hormone and albumin-adjusted calcium, most indicators of bone turnover did not differ significantly throughout the study. There was a modest increase in bone ALP, serum, and urine N-terminal cross-linking telopeptide of type 1 collagen, but bone mineral density did not change significantly at 52 weeks. Further studies are needed to establish the long-term clinical benefit in primary hyperparathyroidism before cinacalcet is recommended as an alternative to surgery.

Panel 2: Differential diagnosis of secondary hyperparathyroidism

Gastrointestinal causes
Inadequate dietary intake
• Food intolerance (milk/lactose)
• Dietary restriction
• Phytates
Malabsorption
• Coeliac disease
• Pancreatic disease
• Inflammatory bowel disease
• Cystic fibrosis
• Gastric bypass surgery
• Corticosteroid treatment
• Ageing
Vitamin D-related causes
Sunlight deprivation
• Pigmented skin in northern latitudes
• Cultural effects, clothing
Dietary restriction
• Strict vegan, lactovegetarian
Liver/biliary disease
• Malabsorption, 25-hydroxylase deficiency, bile salts
Anticonvulsant treatment
• Altered vitamin D metabolism
Vitamin D dependent or resistant rickets or osteomalacia
• Hypophosphataemia

(Continued from previous column)

Kidney
Chronic kidney disease
• Hyperphosphataemia
• 1α-hydroxylase deficiency: decreased 1,25-dihydroxyvitamin D
• Decreased clearance of parathyroid hormone: accumulation of C-terminal parathyroid hormone
• Parathyroid hormone resistance

Cellular/tissue-mediated causes
Bone
• Growth

Genetic
Pseudohyperparathyroidism
• Parathyroid hormone-receptor G-protein abnormal change/parathyroid hormone resistance

“Hungry bone” syndrome

Bisphosphonate treatment
Lactation/post-lactation

Metastatic prostate cancer
Kidney
• Diuretics
• Increased natriuresis
• Idiopathic hypercalciuria
Soft tissues
• Rhabdomyolysis: calcium deposition, hyperphosphataemia, acute renal failure
• Acute pancreatitis
• Sepsis
• Burns
Secondary hyperparathyroidism

Definition and causes

Secondary hyperparathyroidism is the result of failure of one or more components of the calcium homeostatic mechanisms described previously (extrinsic abnormal change). When plasma ionised calcium decreases, the CaSR responds by increasing secretion of parathyroid hormone, resulting in a compensatory mechanism to restore normal function. Under normal circumstances, there is a transient state of relative or absolute secondary hyperparathyroidism. When the parathyroid hormone cannot correct the plasma calcium because of organ failure or reduced calcium availability, hypocalcaemia can occur. Patients might have symptoms and signs related to acute hypocalcaemia or slowly developing hypocalcaemia, and longstanding raised parathyroid hormone.

Panel 2 outlines causes of secondary hyperparathyroidism, and table 3 the associated biochemical profile. The diagnosis is made by obtaining a pertinent clinical history and examination, plus recognition of the combination of plasma albumin-adjusted calcium, phosphate, parathyroid hormone, 25-hydroxyvitamin D, or D₃, and total alkaline phosphatase in each disease. Development of automated immunoassays for parathyroid and 25-hydroxyvitamin D has made it easier to investigate and treat these diseases and to appreciate the role of secondary hyperparathyroidism in the genesis of bone disease, including coeliac disease,⁶⁷ prostatic cancer,⁶⁸ cystic fibrosis,⁶⁹ and bariatric surgery.⁷⁰ Vitamin D deficiency and chronic kidney disease are two areas of major clinical and scientific interest resulting in significant debate, and much controversy in relation to secondary hyperparathyroidism.

Vitamin D deficiency

Differences exist in recommended dietary intakes for calcium and vitamin D between the UK and North America (table 4).⁷¹ In the UK, healthy adults do not require a dietary intake of vitamin D, assuming that they receive sufficient sunlight exposure to maintain adequate circulating concentrations of 25-hydroxyvitamin D. North American recommendations recognise that many elderly people are infirm and housebound, and have little UV exposure; therefore they require increased dietary vitamin D. Recommended calcium intake shows no consistency between countries across all ages. A minimum calcium intake to prevent significant calcium imbalance in men is 450 mg per day and in women 350 mg per day. Surveys of healthy people detect significant secondary hyperparathyroidism in the population (1·2%), with the most frequent causes being low calcium intake and low 25-hydroxyvitamin D.⁷²

The definition of vitamin D deficiency has been much debated. In the past, frank osteomalacia or rickets with obvious clinical signs and symptoms defined vitamin D deficiency. Population studies have correlated the prevailing concentrations of parathyroid hormone and 25-hydroxyvitamin D, showing that as the concentration of vitamin D decreases that of parathyroid hormone increases. Factors such as prevailing renal function, magnesium status, and 1,25-dihydroxyvitamin D are now recognised to have substantial effects on this relation.⁷³ Vitamin D deficiency has also been defined on the basis of increased risk of secondary hyperparathyroidism, high bone turnover, decreased bone mineral density, and the abolishment of seasonal variation in parathyroid hormone.⁷⁴⁷⁵ All these effects have a different threshold concentration of 25-hydroxyvitamin D at which the event accumulates, and as a result the concentration defining vitamin D deficiency varies from 30 nmol/L to 110 nmol/L. As an alternative approach, increasing supplements of vitamin D and calcium were given in one study until the 25-hydroxyvitamin D concentration of 50 nmol/L defined the point at which no further change in parathyroid hormone resulted.⁷⁶ After a review of these heterogeneous data and recognition that most detrimental effects accumulate below 50 nmol/L, Lips⁷⁷ proposed that 25-hydroxyvitamin D concentrations between 25 nmol/L

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Panel 2 outlines causes of secondary hyperparathyroidism, and table 3 the associated biochemical profile.

Table 3: Biochemical measurements in the differential diagnosis of secondary hyperparathyroidism

<table>
<thead>
<tr>
<th>Condition</th>
<th>Albumin-adjusted calcium</th>
<th>Phosphate</th>
<th>Parathyroid hormone</th>
<th>25-hydroxyvitamin D</th>
<th>Total alkaline phosphatase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malabsorption</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Normal/mild high</td>
</tr>
<tr>
<td>Liver failure</td>
<td>Normal/low</td>
<td>Normal/low</td>
<td>Mild high</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Vitamin D deficient</td>
<td>Low</td>
<td>Low</td>
<td>High/very high</td>
<td>Low/very low</td>
<td>High</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Normal/low</td>
<td>High/very high</td>
<td>High/very high</td>
<td>Normal/low</td>
<td>High/very high</td>
</tr>
<tr>
<td>Pseudohypoparathyroidism</td>
<td>Low</td>
<td>High</td>
<td>High/very high</td>
<td>Normal/low</td>
<td>Normal/mild high</td>
</tr>
</tbody>
</table>

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Table 4: Recommended dietary intakes of calcium and vitamin D by age range

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Calcium (UK) (mg/day)</th>
<th>Calcium (North America) (mg/day)</th>
<th>Vitamin D (UK) (IU/day)</th>
<th>Vitamin D (North America) (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 months</td>
<td>340</td>
<td>200</td>
<td>525 (7–12 months)</td>
<td>270 (7–12 months)</td>
</tr>
<tr>
<td>7 months–3 years</td>
<td>280</td>
<td>200</td>
<td>350 (1–3 years)</td>
<td>500 (1–3 years)</td>
</tr>
<tr>
<td>4–50 years</td>
<td>0</td>
<td>200</td>
<td>450–550 (4–10 years)</td>
<td>800 (4–8 years)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>800–1000 (11–18 years)</td>
<td>1300 (9–18 years)</td>
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<td></td>
<td></td>
<td>700/150–50 (19–50 years)</td>
<td>2000 (19–50 years)</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>400</td>
<td>400 (51–70 years)</td>
<td>600 (≥71 years)</td>
<td>700</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1200</td>
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Adapted from reference 91.
and 50 nmol/L be defined as vitamin D insufficient and concentrations less than 25 nmol/L as vitamin D deficient.

Not all authors agree with these analyses and approach. A cohort study from the British National Diet and Nutrition Survey of people aged 65 years and older did not lend support to the notion of a 25-hydroxyvitamin D concentration at which parathyroid hormone unambiguously ceases to decrease. The pattern of changes recorded was different in people older and younger than 85 years, with the decrease in parathyroid hormone attenuated at 35 nmol/L. 25-hydroxyvitamin D in people older than 85 years.

Several assay difficulties exist for 25-hydroxyvitamin D that contribute to the variability in the concentration associated with development of secondary hyperparathyroidism. Immunoassays are easy to use, can be automated, and are very quick to do, but comparisons with high-performance liquid chromatography suggest that significant differences in standardisation and analyte recognition exist between assays, such that assay-specific reference ranges and cut-off values need to be established. Immunoassays seem to be poor at recognising ingested 25-hydroxyvitamin D, and the international vitamin D external quality assessment scheme has drawn attention to issues that occur in several countries.

Despite these limitations, a significant proportion of elderly people in Europe, North America, and Australasia have vitamin D deficiency and secondary hyperparathyroidism. Institutionalised elderly people have a particular high prevalence of both. The risk of falls in some studies is related to the degree of vitamin D deficiency or to secondary hyperparathyroidism, or both. Vitamin D and calcium deficiency resulting in secondary hyperparathyroidism causes increased bone turnover, accelerated bone loss, reduced bone quality, and an increased risk of fracture.

Treatment with calcium and vitamin D or vitamin D analogues can restore parathyroid hormone within the reference range and offers an attractive option to prevent fractures in elderly people. A Cochrane review has concluded that calcium and vitamin D treatment in frail elderly people who are confined to institutions reduces hip and vertebral fractures. Vitamin D alone showed no significant effect on hip fractures, vertebral fractures, or new fractures. A meta-analysis of randomised controlled trials investigating oral vitamin D with or without calcium concluded that vitamin D between 700 IU and 800 IU per day reduces the risk of hip and non-vertebral fractures in ambulatory or institutionalised elderly individuals, whereas 400 IU per day was insufficient for fracture protection. Baseline mean 25-hydroxyvitamin D varies substantially in these studies from 21.3 nmol/L to 76.5 nmol/L (deficient to replete), and changes in 25-hydroxyvitamin D concentration after treatment were equally wide from 10 nmol/L to 65 nmol/L. Optimum fracture protection occurred when mean 25-hydroxyvitamin D increased to 100 nmol/L, suggesting a pharmacological effect of vitamin D supplementation in successful trials.

The Randomised Evaluation of Calcium Or vitamin D (RECORD) trial studied 5292 elderly people aged 70 years and older who had a previous low-trauma fracture and were mobile before the fracture. They were randomly assigned to either oral 800 IU vitamin D, daily, 1000 mg calcium daily, 800 IU vitamin D, plus 1000 mg calcium daily, or placebo. Secondary hyperparathyroidism was detected in 19% (subgroup analysis), and the mean 25-hydroxyvitamin D was 32.5 nmol/L at baseline. The incidence of any fracture did not differ significantly between the groups during 24–62 months of follow-up. In 3314 women aged 70 years and older with one or more risk factors for hip fracture, treatment with 800 IU vitamin D, plus 1000 mg calcium or with dietary advice and falls prevention (control) did not produce any significant difference in hip fractures, clinical fractures, or all fractures over 25 months. Women recruited into a Women’s Health Initiative trial were randomly assigned to receive 400 IU of vitamin D, plus 1000 mg calcium daily or to receive placebo and were followed up for 84 months. The investigators noted a modest but significant increase in bone mineral density at the hip, and an increased risk of renal stones in the treated group. No significant differences were detected in hip, clinical spine, or total fracture incidence.

Overall the data suggest that when a high prevalence of vitamin D deficiency exists, with coincident secondary hyperparathyroidism, then treatment with calcium and vitamin D has a beneficial effect on fracture incidence. However, for most ambulant elderly people, more potent therapies or higher doses of calcium and vitamin D are needed to reduce fracture incidence.

Chronic kidney disease
Secondary hyperparathyroidism occurs in chronic kidney disease as an adaptive response to deteriorating renal function. A combination of factors contribute to the increase in parathyroid hormone that are additive, since glomerular filtration rate (GFR) decreases with progressive stages of disease (table 5). Circulating 1,25-dihydroxyvitamin D begins to decrease in stage 2, and continues to fall as the renal mass decreases and renal 1α hydroxylase enzyme is inhibited by hyperphosphataemia, hyperuricaemia, metabolic acidosis, and 25-hydroxyvitamin D deficiency. As GFR decreases below 60 mL/min/1.73 m², phosphate is retained and stimulates synthesis and secretion of parathyroid hormone. Hypocalcaemia develops as the GFR decreases below 50 mL/min/1.73 m², further stimulating release of the hormone. As GFR decreases further, intact parathyroid hormone (1–84) half-life increases and C-terminal fragments of the hormone...
accumulate. A relative state of end-organ resistance to the hormone exists, but chronic elevation of it has major consequences resulting in bone loss (particularly cortical bone), fractures, cardiovascular disease, and increased mortality.

The term renal osteodystrophy is used to describe a spectrum of bone disease ranging from high bone turnover, usually with excessive secretion of parathyroid hormone, to low bone turnover or adynamic bone disease, associated with normal or low hormone concentration.121 Measurement of intact parathyroid hormone has provided a mechanism whereby subtypes of renal osteodystrophy can be distinguished. Bone biopsy samples and biochemical markers of bone metabolism have been correlated with intact parathyroid hormone. An intact hormone concentration greater than 25–30 pmol/L could indicate the presence of high turnover bone disease, whereas values less than 15 pmol/L are associated with adynamic osteodystrophy.118,119 However, parathyroid hormone resistance varies with progression of chronic kidney disease and dialysis requirement, and some could argue that no adequate surrogate for bone biopsy exists at present.122

In chronic kidney disease, metabolism of parathyroid hormone results in the generation and retention in the circulation of a parathyroid hormone (7–84) fragment. This C-terminal molecule is measured by intact parathyroid hormone assays, resulting in an overestimation of parathyroid hormone (1–84) when fragment (7–84) is present. Whole parathyroid hormone assays have been developed that do not react with fragment (7–84), and by measuring intact parathyroid hormone then subtracting whole parathyroid hormone, an estimate of this fragment can be made. Parathyroid hormone (7–84) can antagonise the calcaemic and phosphaturic actions of parathyroid hormone (1–84) when administered in high concentrations and when abnormal molar ratios exist in animal and cell models.118 Evidence suggests that fragment parathyroid hormone (7–84) can act via a separate parathyroid hormone receptor from parathyroid hormone (1–84) and (1–34) and can result in hypocalcaemia, inhibit formation of bone cells positive for tartrate-resistant acid phosphatase, and interfere with parathyroid hormone (1–84) and (1–34) effects in vivo and in vitro.119–123 Results using the whole and intact parathyroid hormone (1–84) assays are inconsistent. Although advocates for the measurement of whole parathyroid hormone (1–84) in chronic kidney disease exist124 and there are reports of increasing parathyroid hormone fragment (7–84) and increased ratios of intact to whole parathyroid hormone associated with adynamic bone disease in chronic kidney disease,125 several investigators have independently failed to confirm these findings.122–125 At present there is insufficient consistency of evidence to advocate abandoning current intact parathyroid hormone assays in favour of whole parathyroid hormone assays.

### Table 5: Stages of chronic kidney disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73m²)</th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Kidney damage with mild reduction in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Moderate reduction in GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Severe reduction in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

Kidney damage is defined as pathological abnormal changes or indicators of damage, including abnormal changes in blood or urine tests or in imaging studies. GFR=glomerular filtration rate.

### Table 6: Targets for calcium or bone metabolism from the National Kidney Foundation Dialysis Outcomes Quality Initiative

<table>
<thead>
<tr>
<th>Target range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact parathyroid hormone (1–84)</td>
</tr>
<tr>
<td>Serum-adjusted calcium</td>
</tr>
<tr>
<td>Serum phosphate</td>
</tr>
<tr>
<td>Calcium and phosphate product</td>
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</table>

Advances in the treatment of secondary hyperparathyroidism in chronic kidney disease have resulted in guidelines attempting to harmonise the approach to treatment to slow disease progression and prevent complications. Initial guidelines, launched in 1995 by the National Kidney Foundation (NKF) as the Dialysis Outcomes Quality Initiative (DOQI), were developed to improve the delivery of dialysis.126,127 These guidelines served as the basis for national and international discussion and for stimulating research. During guideline development, a greater opportunity (in remit and scope) clearly existed for all patients with chronic kidney disease across all grades of disease, and so a broader scope was addressed and the Kidney Disease Outcomes Quality Initiative (KDOQI) developed.128 Table 6 gives a brief summary of the KDOQI targets related to calcium and bone metabolism. Publication of the KDOQI guidelines resulted in debate about how these aims can be achieved with current treatments. Phosphate can be decreased with binders, with calcium-based binders being the most cost effective. Concerns have been raised regarding their role in progression of cardiovascular and arterial calcification,129 and sevelamer has been recommended as an alternative.130 The Calcium Acetate Renagel Evaluation (CARE) study131 indicated that calcium acetate is more effective than is sevelamer in controlling serum phosphate, calcium and phosphate product, and bicarbonate in patients undergoing haemodialysis; however, sevelamer is associated with slower progression of coronary, aortic, and valvular calcification.132,133 Lowering the calcium concentration of dialysis fluid can help to prevent development of hypercalcaemia in patients with chronic kidney disease, but requires careful monitoring when sevelamer is also used.
Administration of vitamin D analogues such as 1α hydroxycholecalciferol (alfacalcidol) has been advocated in early chronic kidney disease. It prevents progression of bone disease and improves bone histology by reducing secondary hyperparathyroidism.134 When used in stages 3 and 4 chronic kidney disease it is effective in decreasing parathyroid hormone and improving bone mineral density.135 Improvements in clinical, biochemical, and skeletal indices can be seen in patients on haemodialysis.136 Injectable active vitamin D (1,25-dihydroxyvitamin D3; calcitriol) is effective in reducing parathyroid hormone in haemodialysis patients when given intermittently intravenously, but routine use has been restricted because of fears of accelerating progression of chronic kidney disease due to hypercalcaemia, hyperphosphataemia, and hypercalciuria. These fears could be misplaced since injectable vitamin D was shown to increase survival in patients undergoing dialysis, and activation of the vitamin D receptor helped to maintain normal bone formation.137 Paracalcitol (19-nor-1,25-dihydroxyvitamin D3) decreases parathyroid hormone while having minimal hypercalcaemic and hyperphosphataemic effects. Prospective studies and retrospective analysis suggest that paracalcitol is excellent at suppression of parathyroid hormone with a fairly safe side-effect profile, and that it confers a survival advantage while reducing admission rates compared with calcitriol.138

The development of calcimimetics provides a drug class that is useful in the treatment of chronic kidney disease. Placebo-controlled trials have established that cinacalcet significantly reduces secretion of parathyroid hormone in haemodialysis and peritoneal dialysis patients,139 and a randomised, double-blind, placebo-controlled study has shown that it is effective in the treatment of patients with chronic kidney disease who are not receiving dialysis.140 Parathyroid hormone decreases by at least 30% in these studies, and this reduction can be maintained for up to 3 years.141 Preliminary data suggest that treatment with cinacalcet can reduce parathyroidectomy, fracture, and admission to hospital for cardiovascular reasons,142 but further long-term and comparative studies will be needed to fully establish its role in chronic kidney disease. If the KDOQI guidelines are to be met, combinations of treatments will probably be needed across the range of patients with chronic kidney disease.

Tertiary hyperparathyroidism

Although authors debate the existence of tertiary hyperparathyroidism, most believe that it represents a state of autonomous function of parathyroid tissue (intrinsic abnormal change) that is characterised by hypercalcaemic hyperparathyroidism. It is usually the outcome of longstanding secondary hyperparathyroidism and is characterised by a lack of suppression of parathyroid hormone by increasing calcium or vitamin D analogues. CaSR underexpression can be seen resulting in an increase in parathyroid hormone secretory set-point and a depletion of vitamin D receptors.143 Although hyperplastic nodular parathyroid tissue in single or double adenomas is a regular finding, four-gland hyperplasia is more common.134,144

The most common cause of tertiary hyperparathyroidism is longstanding chronic kidney disease. Prolonged stimulation of parathyroid cell growth due to high phosphate, low 1,25-dihydroxyvitamin D, and intermittent hypocalcaemia results in nodular hyperplasia that is characteristic of tertiary hyperparathyroidism. Abnormal glands rarely undergo involution. High secretion of parathyroid hormone and hypercalcaemia can persist in patients after renal transplant (calcium adjusted for albumin is raised in 8–5–65% of cases), although phosphate and vitamin D metabolism significantly improve. Graft function and GFR are important factors determining concentrations of the hormone, but pretransplant duration of dialysis, severity of hyperparathyroidism, and uraemia are contributing factors.

Tertiary hyperparathyroidism can occur in patients with X-linked hypophosphataemic rickets139,145,146 and adult onset (autosomal dominant) hypophosphataemic rickets147 in which long-term treatment with phosphate148 and vitamin D stimulates parathyroid tissue, resulting in hypercalcaemic hyperparathyroidism. High dose oral phosphate increases plasma phosphate, causing a transient decrease in ionised calcium and a decrease in 1,25-dihydroxyvitamin D. This triple combination results in parathyroid stimulation and secretion of parathyroid hormone. A similar situation can arise in patients with oncogenic osteomalacia treated with oral phosphate and vitamin D.149 In both diseases, increased fibroblast growth factor 23 contributes to suppression of 1,25-dihydroxyvitamin D production.150 Total or subtotal parathyroidectomy is recommended treatment for tertiary hyperparathyroidism.111 Some surgeons also advise autotransplantation of parathyroid tissue in an easily accessible site, such as the forearm.

Conflicts of interest

I have lectured for MSD, Lilly, and Proctor and Gamble; and have served on advisory boards for MSD, Lilly, Proctor and Gamble, and Amgen.

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Seminar


