# Clinical cases in advanced chronic kidney disease

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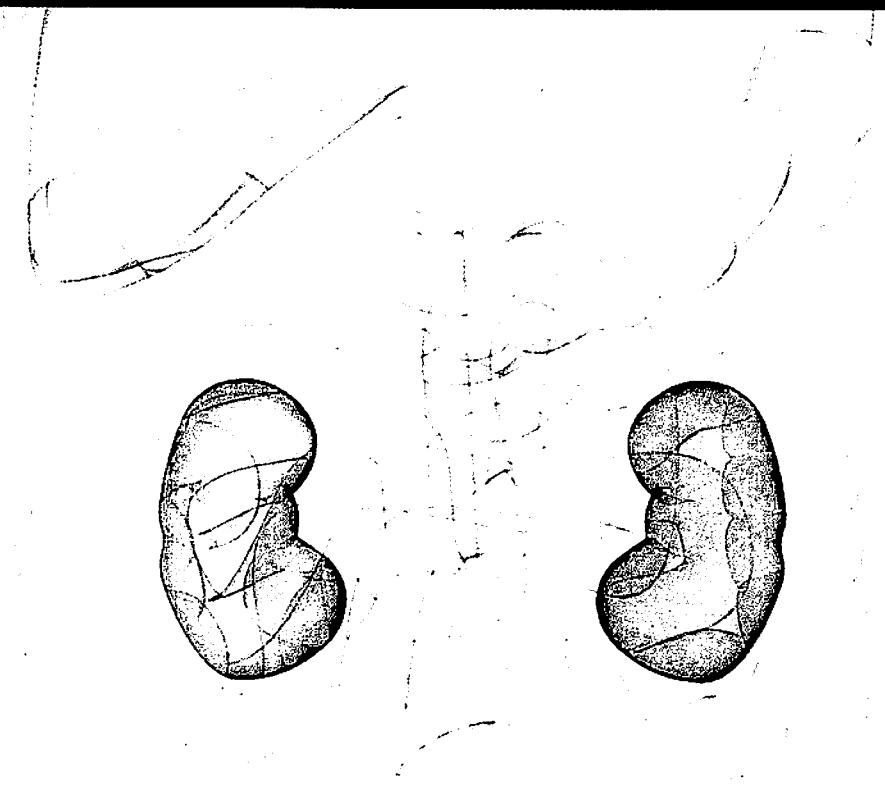

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# Contents

# Assessment and management of parathyroid hyperplasia in secondary hyperparathyroidism

Mario Meola

## Introduction

Secondary hyperparathyroidism (sHPT) is one of the most common and serious complications of chronic kidney disease (CKD) and long-term dialysis. Patients are considered to have severe sHPT when serum calcium, phosphorus, calcium/phosphorous (Ca x P) product, and intact parathyroid hormone (iPTH) levels can no longer be adequately controlled by conventional therapies, and when clinical symptoms are associated with a significantly increased risk of cardiovascular morbidity and mortality [1]. Following international guidelines, parathyroidectomy becomes mandatory when one or more parathyroid glands are greatly enlarged (parathyroid volume >500 $mm^3$), iPTH values are >700 pg/mL, and the response to conventional therapy is poor [2].

## Pathophysiology of secondary hyperparathyroidism

Biochemical abnormalities in CKD cause persistent overstimulation of parathyroid glands, which can change the biology and function of parathyroid cells. Overstimulation of parathyroid cells triggers a process of cell hypertrophy and hyperplasia, leading to the selection of cell clones with reduced expression of calcium and vitamin D receptors (CaR and VDR, respectively) [3]. The pattern of cell growth is initially that of diffuse polyclonal hyperplasia, which can be followed by monoclonal nodular hyperplasia after longstanding parathyroid overstimulation. Parathyroid glandular volume is associated with secretion of PTH and severity of sHPT, showing a linear correlation between PTH levels and glandular volume in glands that do not exceed 2000–3000 $mm^3$ (~2–3 g) [4]. With continued growth, the largest glands tend to disengage from the receptor control mechanisms – that is, upregulation of CaR and VDR – and grow independently. These glands appear to release PTH at levels unrelated to total glandular volume.

### Imaging

Owing to the location of the parathyroid glands, their generally small size and the difficulty in obtaining accurate measurements of glandular volume with common non-invasive techniques, only indirect measurements of parathyroid gland volume are possible. However, ultrasonography with colour Doppler (US/CD) imaging can localise hyperplastic parathyroid glands. US/CD is the only technique that accurately measures volumetric variations of the parathyroid glands and simultaneously provides semi-quantitative parameters on glandular perfusion.

### Traditional treatment of secondary hyperparathyroidism

Surgical parathyroidectomy is traditionally the ultimate treatment for sHPT that is resistant to medical therapy, but advances in ultrasonographic techniques have increased the range of management options. When performed by skilled operators, US/CD can localise hyperplastic parathyroid glands that become hypoechoic and are well distinguished from the thyroid parenchyma, owing to their increased cellularity and the reduction of the number of fat cells within the parathyroid tissue. The use of serial determinations of glandular volume and perfusion pattern allows us to evaluate the progression of sHPT to the same extent as is possible with the use of biochemical parameters [5,6].

### Presentation

The patient in this scenario is a 51-year-old woman who has been receiving maintenance haemodialysis since 1981. At birth, she was diagnosed with bladder exstrophy with vesicoureteral reflux and underwent reconstructive surgery of the bladder neck and replanting of the ureters. At the age of 12 years, and after several episodes of recurrent urinary tract infections, she was found to have a severely compromised glomerular filtration rate (GFR), with a serum creatinine level of 2.5 mg/dL. Cystography showed a bilateral vesicoureteral reflux with grade IV hydronephrosis. Urography showed enlarged kidney shadows with irregular profiles, suggesting the presence of multiple renal scars and corticalisation of calices. A uretero-sigmoid cutaneostomy was performed, but GFR became progressively worse. At the age of 22 years, when serum creatinine was 12 mg/dL, she started maintenance haemodialysis and received a continuous oral therapy with $CaCO_3$ 4 g/day.

### Progression with inital therapy

Severe sHPT typically develops over a long period of dialysis, as is evident in this patient's history (Table 9). Despite treatment with conventional therapy, the patient showed a progressive increase in glandular volume and in the number of glands seen with UC/SD

imaging. By the end of 2003, the patient was a candidate for parathyroidectomy, but she refused this procedure.

**Table 9. Laboratory data, imaging findings and treatments received**

| Year | Laboratory findings | US/CD findings | Treatment decision |
|---|---|---|---|
| 1990 | Ca: 11 mg/dL<br>P: 4.9 mg/dL<br>Ca x P: 49 $mg^2/dL^2$<br>iPTH: 611 pg/mL<br>ALP: 580 IU/L | Nodular hyperplasia of the right inferior parathyroid gland; volume: 2323 $mm^3$ | Chemical ablation of parathyroid hyperplasia with percutaneous ethanol injection |
| 1990 | iPTH: 795 pg/mL<br>ALP : 952 IU/L | Right inferior gland: 3312 $mm^3$ | |
| 1993 | | Right inferior gland: 4260 $mm^3$<br>Left hypoechoic gland: 31 $mm^3$ | Vitamin D (4 µg/week); $CaCO_3$ reduced to 2–3 g/day |
| 1994–1996 | iPTH: 670-450 pg/mL<br>ALP: 400-265 IU/L | Right inferior gland: 4556 $mm^3$<br>Left gland: 81 $mm^3$<br>Radiotracer hyperaccumulation near right inferior pole of the thyroid | Oral calcitriol replaced by intravenous calcitriol 1.5 µg 3 times/wk; $CaCO_3$ stopped; $Al(OH)_3$ added (3 tablets twice/week) |
| 1997–2003 | Ca: 12.3 mg/dL<br>P: 5.6 mg/dL<br>Ca x P: 68.8 $mg^2/dL^2$<br>ALP: 326 U/L<br>iPTH: 1350 pg/mL | Right inferior gland: 5299 $mm^3$<br>Left gland: 210 $mm^3$<br>Gland at the inferior pole of the left thyroid lobe: 65 $mm^3$ | Calcitriol interrupted owing to episodes of hypercalcaemia and hyperphosphataemia; parathyroidectomy indicated but not performed, owing to patient refusal |

Abbreviations: ALP, total alkaline phosphatases; Ca x P, calcium/phosphate product; iPTH, intact parathyroid hormone; US/CD, high-resolution ultrasonography with colour Doppler.

In January 2005, calcitriol was replaced by intravenous paricalcitol 5 µg/week, sevelamer 4800 mg/day, and $CaCO_3$ 2 g/day. Six months after beginning paricalcitol, the patient's biochemical parameters continued to show evidence of severe sHPT:

- Calcium: 10.5 mg/dL
- Phosphate: 5 mg/dL
- Ca x P: 52.5 $mg^2/dL^2$
- bALP: 1243 U/L
- iPTH: 1600 pg/mL

In this patient, the maximum degree of severity of sHPT and resistance to conventional therapy coincided with the presence of four hyperplastic, hypoechoic and hypervascularised glands, as shown with US/CD (Figure 12).

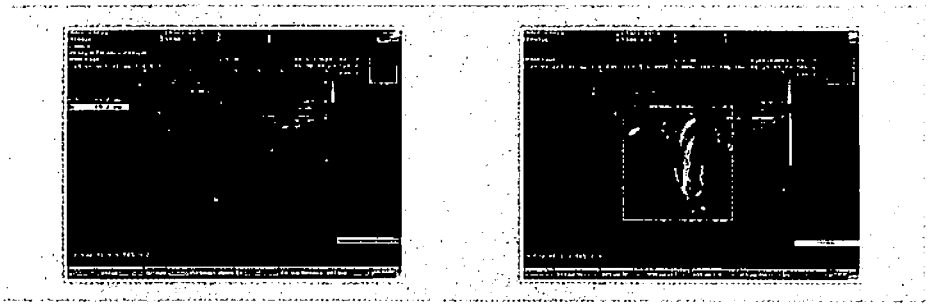
### Rationale for cinacalcet treatment

Calcimimetics help to control several biochemical markers of sHPT, including serum calcium, phosphate, and calcium/phosphate product, as well as parathyroid hormone and alkaline phosphatases. Long-term treatment with calcimimetics and conventional therapy also reduces parathyroid hyperplasia in patients with severe sHPT [7].

### Outcomes with cinacalcet

In July 2005, cinacalcet was added to conventional therapy, with a maximum dosage of 150 mg/day (Figure 13). Between 2007 and 2009, the patient's mineral metabolism parameters tended to be within the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) targets [2]. During this period, the dosage of each drug was dynamically modulated in relation to the values of calcium, phosphorus, Ca x P product, alkaline phosphatases, and iPTH, according to the OPTIMA algorithm [8]. By January 2010, her biochemical parameters had improved markedly (Table 10).

**Figure 12. Progression of sHPT and parathyroid hyperplasia despite conventional therapy**



High-resolution ultrasonography with colour Doppler imaging shows that the maximum degree of severity of secondary hyperparathyroidism and resistance to conventional therapy coincided with the presence of four hyperplastic, hypoechoic and hypervascularised glands. Images printed with permission from Mario Meola.

**Table 10. January 2010 biochemical findings**

| Parameter | Value |
|---|---|
| Ca | 8.6 mg/dL |
| P | 5 mg/dL |
| Ca x P | 43 $mg^2/dL^2$ |
| ALP | 316 IU/L |
| iPTH | 360–400 pg/mL |

Abbreviations: Ca x P, calcium/phosphate product; ALP, total alkaline phosphatases; iPTH, intact parathyroid hormone.

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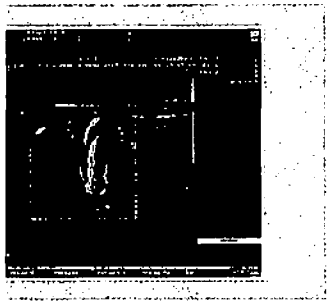

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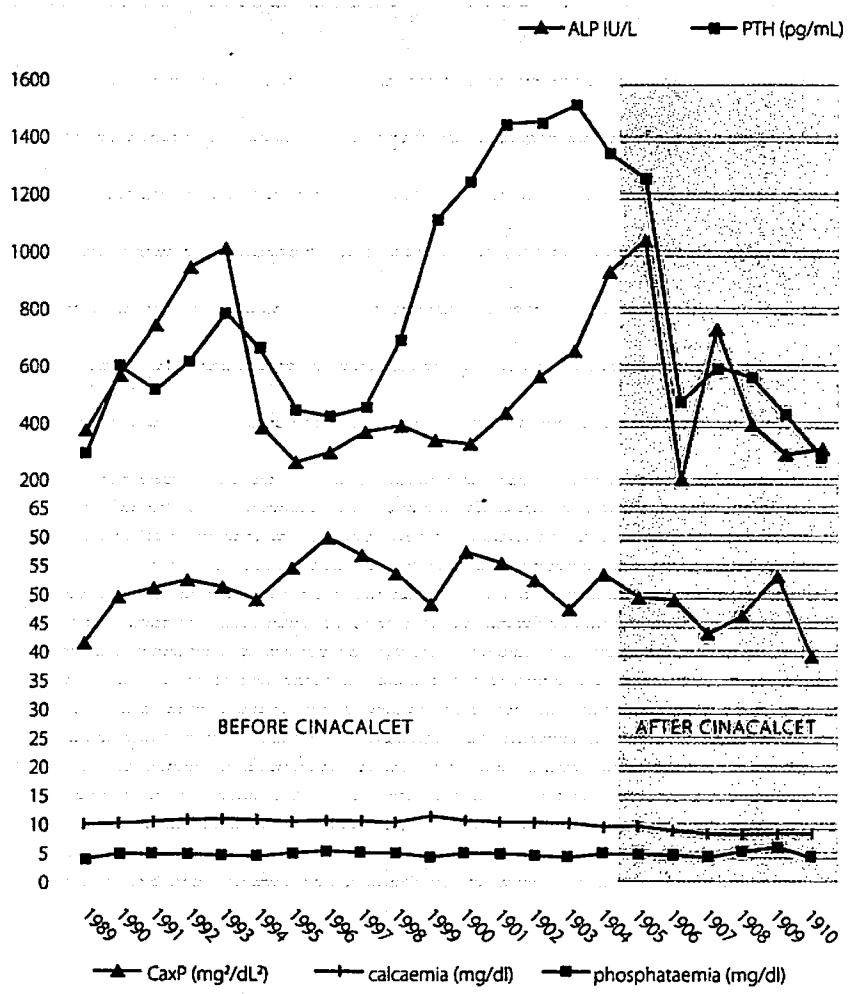
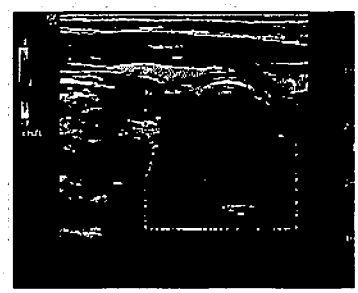
Calcimimetics may be able to modulate the biological response of the parathyroid cell by direct stimulation of the calcium receptor and by an indirect improvement of the sensitivity and expression of the vitamin D receptor [9]. In addition, the synergic action of calcimimetics and vitamin D with phosphate binders on receptor stimulation may promote the regression of morphological sHPT. Some reports indicate that calcimimetics may also reduce parathyroid volume by enhancing cell apoptosis [10]. In this patient,

**Figure 13. Addition of cinacalcet to standard therapy improved biological markers of sHPT**




Abbreviations: ALP, alkaline phosphatase; PTH, intact parathyroid hormone; Ca x P, calcium/phosphate product.
Figure printed with permission from Mario Meola.

**Figure 14. Reduction in parathyroid glandular volume**



High-resolution ultrasonography with colour Doppler shows that the right inferior parathyroid gland decreased in size from 5299 $mm^3$ in 2005 to its current size of 3979 $mm^3$, suggesting regression of hyperplasia. Image printed with permission from Mario Meola.

US/CD imaging shows that the right inferior parathyroid gland decreased in size from 5299 $mm^3$ in 2005 to its current size of 3979 $mm^3$, suggesting regression of hyperplasia (Figure 14). The morphological and vascular patterns of the gland are unchanged.

Volumetric variations of the other parathyroid glands before and after the addition of cinacalcet are shown here (Figure 15). The mediastinal parathyroid gland is hyperechoic and measures 47 $mm^3$, the left superior parathyroid gland is 214 $mm^3$ and has poor vascularisation, and the left inferior is no longer distinguishable from the thyroid parenchyma.

## Discussion

Secondary hyperparathyroidism is one of the most common and serious complications of CKD. Progression of sHPT is a slow and continuous process that often occurs despite conventional therapy. Although parathyroidectomy is the ultimate treatment for sHPT that is resistant to medical treatment, recent advances in ultrasonographic techniques have increased the range of management options. US/CD is a valuable tool for monitoring morphological and vascular changes of hyperplastic parathyroids in response to new therapies. By providing information on both the progression and regression of hyperplasia, US/CD findings also inform clinical, pharmacological and surgical decision making. The availability of calcimimetics has helped to change the natural history of clinical sHPT, and it may change the therapeutic utility of parathyroidectomy.

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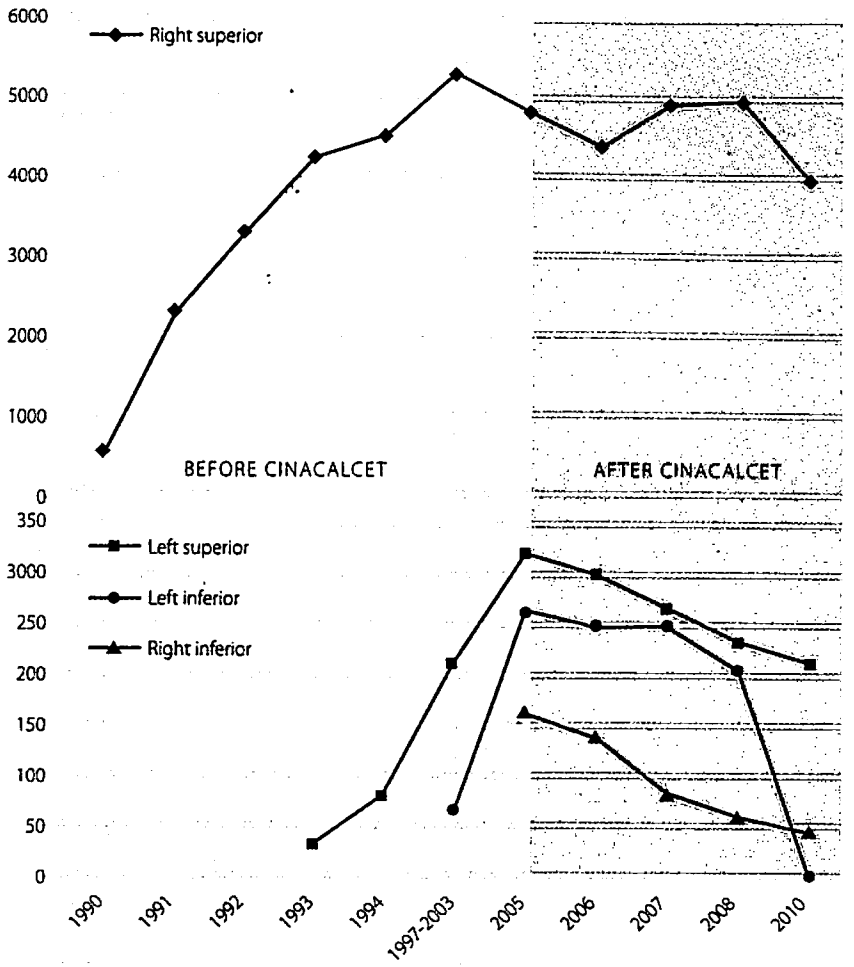
**Figure 15. Volumetric variations of parathyroid glands after cinacalcet treatment**

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## Summary

This 51-year-old patient developed severe sHPT marked by parathyroid hyperplasia and a total glandular volume of approximately 6000 mm³ (~ 6 g), despite long-term treatment with conventional therapy. Progression of sHPT was stopped only when cinacalcet was added to her treatment regimen. Treatment with cinacalcet reduced PTH serum levels and stabilised mineral metabolism, allowing the patient to avoid parathyroidectomy.

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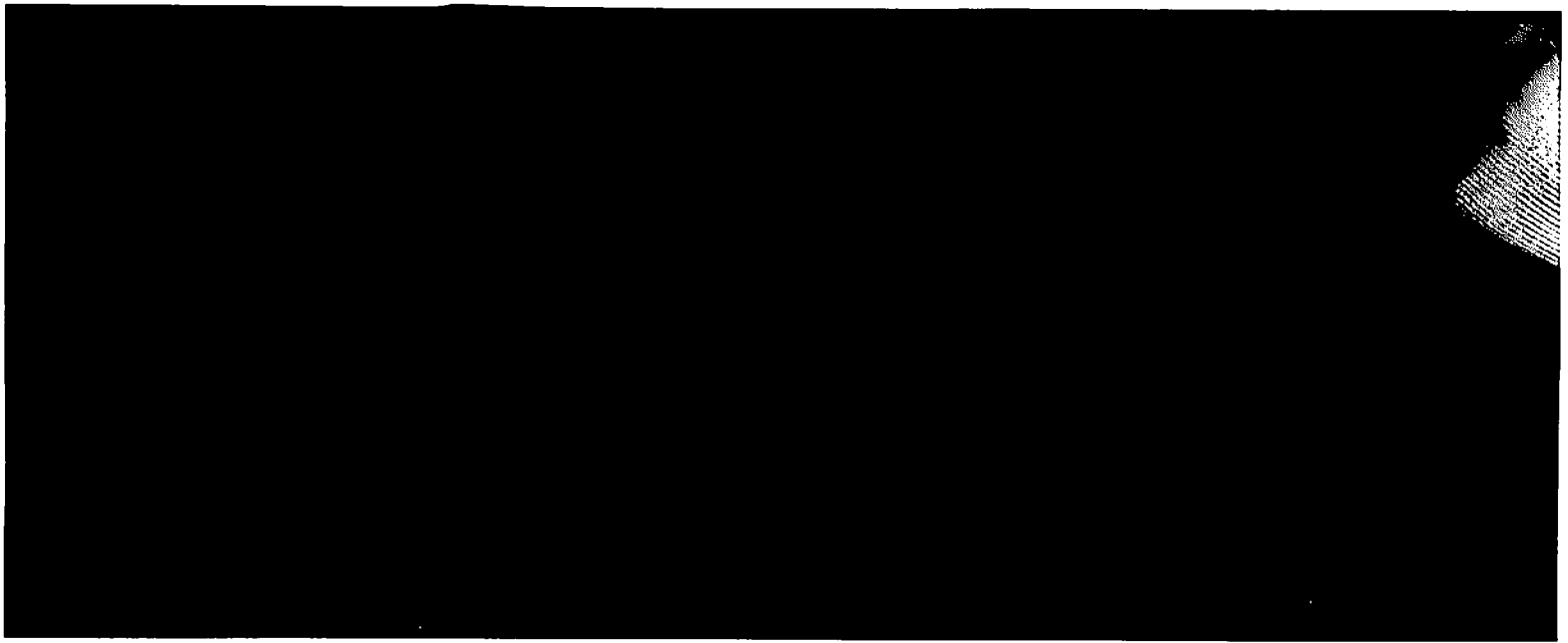

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