Primary hyperparathyroidism: just how 'primary' is it really?

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Hyperparathyroidism: causes and definitions

Hyperparathyroidism (HPT) is a biochemical diagnosis defined by the serum level of intact parathyroid hormone (PTH) above laboratory reference range. It has long been subclassified into three forms. Primary hyperparathyroidism (PHPT), whose management is discussed in the elegant and informative review by Ayuk and colleagues [Ayuk *et al.* 2010], results from a primary defect of autonomous PTH secretion and is defined biochemically when HPT is accompanied by hypercalcaemia and, depending on vitamin D sufficiency, hypercalciuria. It is almost invariably an acquired disease (even if genetically programmed, for example, due to mutations in *MEN1*, *RET*, *HRPT2* and *HNF1B*) [Oram *et al.* 2010; Sharretts and Simonds, 2010], resulting from parathyroid gland hyperplasia or neoplasia (typically adenoma, but rarely carcinoma) [Ayuk *et al.* 2010]. Severe neonatal HPT can occur with biallelic or severe heterozygous inactivating mutations of the extracellular calcium sensing receptor (CaSR) [Pearce *et al.* 1995]. Most *CASR* heterozygotes manifest milder hypercalcaemia with HPT, familial benign hypercalcaemia with hypocalciuria (FBHH), which can be mistaken for PHPT if the calcium/creatinine clearance ratio (to evidence/refute hypercalciuria) has not been ascertained. Crucially, FBHH does not exhibit the adverse skeletal and extraskeletal manifestations of PHPT, nor does it respond to subtotal parathyroidectomy.

Secondary HPT (SHPT) represents the physiological response of normally functioning parathyroid glands to suboptimal levels of bone minerals and/or 1,25-dihydroxyvitamin D (1,25OHD). In the developed world it is most typically found in patients with vitamin D insufficiency

(though the threshold and gradient of PTH secretion with increasing degrees of insufficiency vary widely between individuals) [Frost *et al.* 2010; Rejnmark *et al.* 2010] and/or deficient 1-alpha hydroxylase activity, most typically seen in chronic kidney disease (CKD) stage 4 and above. In the developing world, SHPT is observed among the very poor, whose diets are so deficient in bone minerals that even high circulating levels of UVB-photosynthesised calciferol (vitamin D₃) cannot compensate [Aspray *et al.* 2005]. In the developed world, such a biochemical picture is only seen with severe malabsorption and/or inherited disease, such as hypophosphataemic rickets resulting from genetic defects in the fibroblast growth factor 23 (FGF23)-mediated phosphaturic pathway [Bergwitz and Juppner, 2010].

Tertiary HPT (THPT) can occur in patients with longstanding SHPT from end-stage renal disease (ESRD), but is also sometimes observed in patients who previously had ESRD and whose renal function has normalized after renal transplantation [Guerra *et al.* 2010]. Although biochemically (and ultimately histologically) indistinguishable from PHPT, the picture that emerges from longitudinal follow up is chronic homeostatic stimulation of parathyroid chief cells, leading to clonal expansion and, eventually, autonomous PTH secretion resulting from parathyroid hyperplasia and/or adenomatous transformation [Arnold *et al.* 1995]. THPT, sporadic PHPT and genetically based PHPT are histologically indistinguishable. A key aim in moderate to severe chronic renal impairment is to reduce the rate at which transformation from secondary to tertiary HPT occurs, through judicious PTH suppressive therapy with calcium and 1-alpha-hydroxylated vitamin D analogues.

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Whether native vitamin D retains a role in bone mineral balance in the anephric patient remains a matter of controversy and active research [Jean *et al.* 2008]. However, even in the best hands, a proportion of patients still end up developing THPT, requiring surgical parathyroidectomy. Cinacalcet is certainly effective in treating THPT when the patient declines surgery, is too frail to undergo surgery, or surgery has not been entirely successful. The addition of cinacalcet to standard therapy in patients with SHPT might reduce the rate of progression to THPT, but currently there are insufficient long-term efficacy and cost-effectiveness data, although early data appear promising [Block *et al.* 2010].

Case-driven changes to hyperparathyroidism management in Newcastle-upon-Tyne

Over the past 2 years a series of patients with biochemical PHPT presenting to our unit have contributed to a steep personal learning and driven progressive changes to how the condition is managed in Newcastle-upon-Tyne, UK. By briefly presenting some salient cases that accrued to one author (RQ) that were extensively discussed with the coauthors, we hope to share these new insights and also illuminate the process by which these changes emerged.

Case 1

A 41-year-old woman underwent right lower parathyroidectomy for PHPT associated with radiologic nephrocalcinosis and subperiosteal erosion of several digits. Histology revealed parathyroid carcinoma, evidenced by capsular invasion with fibrosis, trabecular pattern, and frequent mitotic figures [Schantz and Castleman, 1973]. Postoperatively she remained consistently normocalcaemic, with serum calcium levels (adjusted for serum albumin concentration – aCa) 2.19–2.43 mmol/l (normal range 2.12–2.60), normal renal function and normal bone chemistry under long-term follow up. However, at age 50, her PTH level was found to be elevated at 74 ng/l (normal range 10–60), which generated understandable anxiety in her primary care physician. There was no clinical or sonographic evidence of disease recurrence, so it appeared likely that HPT was a secondary phenomenon, even though her serum 25OHD level was in the ‘healthy range’ [Pearce and Cheetham, 2010] at 80 nmol/l (optimal >75 nmol/l). She was therefore started on daily oral calcium (194 mg) and ergocalciferol (vitamin D₂: 800 IU = 20 µg) and, on review 6 months later,

her PTH level had fallen to 44 ng/l with a 25OHD level of 87 nmol/l.

This woman clearly has an unusually high serum 25OHD and/or bone mineral intake threshold for suppression of PTH secretion, presumably related to diet and/or genetic predisposition.

Case 2

A 43-year-old woman was diagnosed with PHPT whilst living in New York (latitude 40.5° north) when she presented with a right kidney stone. She elected for observation-only management because of sonographic nonlocalization of any discrete adenoma and concern that even mild postsurgical vocal cord dysfunction might adversely affect her performance as a flautist. Endocrine follow up was transferred when she moved to Newcastle-upon-Tyne (55° north) aged 47. Renal function and bone chemistry were normal except for a serum aCa level of 2.71 mmol/l and a PTH level of 146 ng/l, but her calcium/creatinine clearance ratio calculated from a contemporaneous 24 h urine specimen was remarkably low at 0.004, suggesting FBHH rather than PHPT. However, as her serum 25OHD level was also low (22 nmol/l), it was decided to repeat her investigations once she was assessed as less vitamin D deficient. After 6 months of treatment with colecalciferol (vitamin D₃: 1000 IU = 25 µg) daily, her 25OHD level appeared ‘healthy normal’ at 82 nmol/l. Her aCa level had fallen slightly to 2.64 mmol/l, her PTH level to 83 ng/l, and the calcium/creatinine clearance ratio was now clearly consistent with PHPT at 0.02. Owing to osteopaenia on bone densitometry and persistent (albeit reduced) musculoskeletal symptoms, she underwent right inferior parathyroid adenomectomy at age 49. Eighteen months later she remains in biochemical remission, taking vitamin D replacement in the winter months.

This case shows that urine calcium clearance values cannot reliably inform the diagnosis of PHPT *versus* FBHH when the vitamin D status is either not known or is known to be suboptimal. Vitamin D deficiency is particularly prevalent in the UK because of the northern latitude, ubiquitous cloud cover, lack of statutory fortification of food/milk and, arguably, a longstanding, high-profile ‘skin cancer prevention’ campaign [Gillie, 2010; Pearce and Cheetham, 2010; Hyppönen and Power, 2007]. Also intriguing was the observation that both aCa and PTH

levels actually fell on vitamin D₃ replacement. Although clinicians are intuitively concerned about exacerbating or 'unmasking' PHPT with vitamin D replacement [Hannan *et al.* 2004], there are no credible reports of this ever having occurred with physiological doses of native vitamin D alone (as opposed to hydroxylated vitamin D analogues), without concomitant calcium supplementation [Grey *et al.* 2005].

Case 3

An 85-year-old woman who was an inpatient with musculoskeletal symptoms associated with biochemical PHPT was referred for endocrine advice: her aCa level was 2.73 mmol/l, with otherwise normal renal function and bone chemistry, her PTH level was 150 ng/l, and her 25OHD level was 14 nmol/l. Her team were advised to start her on colecalciferol 10,000 IU weekly and to repeat a full bone chemistry profile 6 weeks later. This showed that her aCa level had fallen to 2.62 mmol/l and her PTH level to 86 ng/l; her urine calcium/creatinine clearance ratio was calculated to be 0.017. As she was symptomatically improved and her bone chemistry markers were all moving in the right direction, it was decided to continue medical therapy and review her progress in the endocrine clinic 3 months later.

When she attended clinic it emerged that she had already undergone right inferior parathyroidectomy the month before, for which the histology was more suggestive of parathyroid hyperplasia than adenoma. Her postoperative aCa level was 2.42 mmol/l, her 25OHD level was 58 nmol/l, but her PTH level was unchanged at 87 ng/l. Colecalciferol therapy was reinstituted and, over the following 6 months, she remained normocalcaemic and, with optimization of her vitamin D status (25OHD = 92 nmol/l), her PTH level also normalized (58 ng/l). Taking into account the

histologic findings, the improvements in bone chemistry with vitamin D replacement were so striking that one inevitably wonders whether her bone chemistry might have continued to improve over time even without surgery.

Case 4

A 47-year-old postmenopausal woman was referred with musculoskeletal symptoms associated with biochemical PHPT and raised serum alkaline phosphatase (Alk P: 154 IU/l, normal range 35–120), a PTH level of 139 ng/l, with normal renal function. Sonography was suggestive of a right inferior parathyroid adenoma, but this could not be confirmed with scintigraphy. Although there was no nephrocalcinosis, DEXA bone densitometry demonstrated osteopaenia at all sites, so she appeared to be a candidate for parathyroid surgery. However, her vitamin D level was clearly suboptimal (see Table 1) and it emerged that, following excision of what ultimately proved to be a benign skin lesion 4 years previously, she had been routinely applying high-SPF sunscreen to exposed areas of skin (a habit that proved impossible to break).

Although the diagnosis of PHPT appeared secure, there was concern that she might be at increased risk of resistant postoperative hypocalcaemia (hungry bone disease) unless hypovitaminosis D was corrected preoperatively. She was therefore started on colecalciferol 10,000 IU weekly and her bone chemistry monitored (see Table 1). By 3 months, her Alk P level had normalized; by 8 months, she was normocalcaemic and her musculoskeletal symptoms had resolved. Surgery has been postponed indefinitely, but the colecalciferol dose has been doubled because of persisting HPT

Case 5

A 65-year-old woman with rheumatoid arthritis, treated with disease-modifying agents

Table 1. Case 4.

	Baseline	3 months	8 months
aCa (mmol/l)	2.82	2.66	2.49
Alk P (IU/l)	154	102	119
PTH (ng/l)	139	88	86
25OHD (nmol/l)	37	68	59
Urine calcium/creatinine clearance ratio	0.012		0.015
Colecalciferol dose (IU/week)	0	10,000	10,000
25OHD, 1,25-dihydroxyvitamin D; aCa, albumin concentration; Alk P, alkaline phosphatase; PTH, parathyroid hormone.			

(azathioprine, rituximab and methylprednisolone), was referred from a rheumatology clinic with incidentally identified PHPT, but otherwise normal renal function and bone chemistry. She was osteopaenic at the spine and hip, with severe forearm osteoporosis. There was no nephrocalcinosis, but sonography and scintigraphy were concordant for a right inferior parathyroid adenoma. Her serum 25OHD level was around the population mean for the end of winter in northern England [Hyppönen and Power, 2007], but experience with the previous cases informed an individual patient therapeutic trial of vitamin D therapy in the form of colecalciferol 20,000 IU monthly, with careful monitoring of bone chemistry by the rheumatology team (see Table 2).

Cases 4 and 5 suggest that, even in the context of mild vitamin D insufficiency, PHPT might be fully reversible with vitamin D replacement. These patients continue under clinical review and one might anticipate that their PTH levels will eventually normalize once serum levels of 25OHD have risen above 75–100 nmol/l.

Discussion

Ayuk and colleagues [Ayuk *et al.* 2010] reasonably conclude that the mainstay of therapy for PHPT remains surgery and that long-term medical therapy (with cinacalcet) is expensive and lacks a complete evidence base in terms of hard endpoints such as fracture. However, frail elderly patients with biochemically mild PHPT do represent a therapeutic conundrum. They may be unfit for or unwilling to undergo surgery. It may also be impossible to disentangle relative contributions of advancing age and concomitant accumulating disease burden from putative adverse effects of chronic hypercalcaemia on both neurocognitive dysfunction and physical frailty. Such patients have a high prevalence of diuretic-treated cardiac

disease and may exist in a delicate equilibrium between fluid overload and intravascular volume depletion, either of which can result in recurrent (expensive) hospitalizations with intercurrent (or iatrogenic) episodes of calcaemic decompensation. A pragmatic approach might be to prescribe a time-limited period of cinacalcet therapy and then assess individual clinical responses. A significant functional improvement and/or reduction in hospital admissions might indicate that continuation of therapy will be cost effective overall. Moreover, objective improvement in patient clinical status could potentially allow the surgical option to be revisited.

The cases presented in this article represent a snapshot of one author's (RQ) rapidly evolving clinical practice in PHPT. A complete patient series needs to be analysed and, ultimately, a randomized clinical trial of vitamin D supplementation in PHPT should be undertaken. Nevertheless, these cases raise the intriguing possibility that PHPT may represent the end result of chronic SHPT associated with hypovitaminosis D; that is, PHPT is a variant of THPT arising in patients without CKD.

That autonomous PTH secretion can arise as result of chronic SHPT associated with *absolute* hypovitaminosis D should come as no great surprise given that THPT can develop in patients with CKD after years of SHPT associated with *functional* hypovitaminosis D. However, the extent to which hypercalcaemia and PTH hypersecretion could be 'rolled back' in selected patients after only a few months of vitamin D supplementation would not have been readily predictable *a priori*. But how does one account for the phenomenon of *persisting* HPT in patients with CKD even after successful renal transplantation [Guerra *et al.* 2010]? The answer to this may lie in the ubiquity of hypovitaminosis

Table 2. Case 5.

	Baseline	4 months	8 months
aCa (mmol/l)	2.71	2.56	2.30
Alk P (IU/l)	118	90	80
PTH (ng/l)	140	109	99
25OHD (nmol/l)	46	65	57
Urine calcium/creatinine clearance ratio	0.012	0.013	0.008
Colecalciferol dose (IU/week)	0	5000	5000
25OHD, 25-hydroxyvitamin D; aCa, Calcium adjusted for serum albumin concentration; Alk P, alkaline phosphatase; PTH, parathyroid hormone.			

D among renal transplant recipients [Marcén *et al.* 2009], which may in turn relate to mandatory sunlight-avoidance strategies recommended for patients taking immunosuppressive drugs [Ulrich *et al.* 2009].

In summary, sporadic (i.e. nongenetically programmed) PHTP shares so many of the features of THPT of CKD that it may no longer be useful to categorize them separately. That hypovitaminosis D is ubiquitous among patients with PHPT has long been recognized in the Indian subcontinent [Harinarayan *et al.* 1995], but western physicians have perhaps been slower to recognize this. Moreover, hypovitaminosis D is likely to represent a significant precondition for developing PHPT, with individuals having the lowest thresholds and steepest gradients of PTH secretion in response to hypovitaminosis D being conceivably at highest risk (Figure 1).

However, without longer follow up and randomized clinical trials, a number of elements remain unresolved. For instance, is there a 'window of opportunity' for reversing vitamin D deficiency-associated PHPT, which partially or completely

closes with chronicity? Is progressive loss of PTH secretory autonomicity on vitamin D replacement accompanied by physical involution of hyperplastic/adenomatous parathyroids on serial imaging? Is there a level of hypercalcaemia beyond which vitamin D replacement therapy is unlikely to make any useful impact? Does transient, severe postoperative hypocalcaemia ascribed to 'hungry bone disease' relate to undiagnosed/untreated preoperative hypovitaminosis D? Finally, 'normocalcaemic primary hyperparathyroidism' is a potentially new diagnostic entity that is increasingly gaining traction [Tordjman *et al.* 2010], but to what extent can it be more logically explained by simple hypovitaminosis D and/or deficient intake of bone minerals?

Over the past decade, a principal thrust of vitamin D-related clinical research has been in relation to the multiplicity of nonbone-associated pathologies, such as multiple sclerosis, type 1 diabetes and most major cancers [Pearce and Cheetham, 2010]. So it does seem ironic that this, the latest putative association represents a return to examining the impact of chronic vitamin D deficiency on bone disease.

Figure 1. Schematic illustration of stimuli that promote autonomous PTH secretion and, ultimately, development of parathyroid gland adenoma over time. CaSR, calcium sensing receptor; VDR, vitamin D receptor.

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