Parathyroid pathophysiology in uraemia

J. Cunningham
Department of Nephrology, The Royal London Hospital & Medical College, London, UK

Introduction

Hyperparathyroidism is a frequent and sometimes disabling complication of uraemia. Chronicity of uraemia is a major determinant of the likelihood of hyperparathyroidism which is seen in large numbers of dialysis patients, regardless of treatment modality, as well as in a significant proportion of non-dialysed patients with chronic renal insufficiency [1]. Hyperparathyroidism also spills over into renal transplantation—while rarely developing de novo following successful transplantation, longstanding parathyroid overactivity and hyperplasia as a result of previous dialysis often leads to significant morbidity following successful transplantation [2].

Determinants of parathyroid status in uraemia

The uraemic environment constitutes an extremely complex array of metabolic disturbances. Some components of this have been clearly identified as being of importance in the genesis of hyperparathyroidism. However it is certain that our present understanding is incomplete and it is extremely likely that in the future other previously unrecognized aspects of uraemia will be shown to be of importance. The following discussion will focus on six principle components of the uraemic state that have definite or probable involvement in the development of parathyroid disease. All are linked with varying degrees of interdependency. They are:

(1) reduction (or threatened reduction) of extracellular fluid (ECF) calcium concentration;
(2) aberrant parathyroid response to ECF calcium concentration;
(3) disturbed calcitriol synthesis and action;
(4) disturbed parathyroid hormone (PTH) action;
(5) phosphate retention;
(6) acidosis.

Reduced or threatened reduction of ECF calcium concentration

ECF calcium concentration is within the normal range in the majority of uraemic patients. However the uraemic environment exerts downward pressure on ECF calcium, which requires the support of compensatory mechanisms to remain within the normal range. The direct threat to calcium comes from calcitriol deficiency (relative or absolute) and phosphate retention, the latter central to the "trade off" hypothesis of Slatopolsky and Bricker [3]. Compensation comes principally from an increase in PTH secretion.

Aberrant parathyroid response to ECF calcium concentration

An important question is whether or not the parathyroid glands respond aberrantly to ambient calcium concentration in uraemia. Several lines of evidence suggest that such aberration does indeed exist, although the literature is not entirely consistent in regard to this. Early studies by Brown et al. [4] using human parathyroid cells in vitro showed that cells from pathological glands (uraemic hyperparathyroidism or primary hyperparathyroidism) were less readily suppressed by calcium than were cells from normal glands. The immediate explanation for this discrepancy was not immediately apparent, and remains uncertain. A membrane-located calcium sensor has been identified recently [5] and it is possible that one or more components of uraemia modify this receptor in a manner such as to reduce the sensitivity of the parathyroid cells to calcium. Although this is an attractive hypothesis that would explain a number of experimental and clinical observations, direct evidence of a change in calcium sensor function is lacking.

Several groups have probed the relationship in vivo between calcium and parathyroid cell function in uraemia by acutely perturbing ECF calcium concentration and following the resulting PTH response. Many, but not all, of these studies have suggested that the administration of calcitriol leads to an increase in the suppressibility of the parathyroids by calcium. Unfortunately virtually all have methodological flaws and interpretation is further hindered by differences in the protocols used and techniques of data analysis.
Parathyroid paraphysiology in uraemia

For example others and ourselves have used acute hypercalcaemia and hypocalcaemia during dialysis sessions as a means of effecting the calcium perturbation. Results obtained in this way may well be confounded by parallel changes of phosphate concentration and/or pH, both of which may have independent effects on parathyroid function (vide infra). The concept of a parathyroid 'set point' for calcium has been proposed as a measure of calcium sensitivity, but the precise biological relevance of set point, and indeed some other derived parameters such as PTHmax, PTHmin, slope with or without log transformation, or factoring for PTHmax, is open to question. This area has been extensively reviewed by Felsenfeld and Llach [6].

In addition to disturbances of the acute parathyroid response to changes in calcium, we need to consider also the impact of ECF calcium on two other important aspects of parathyroid function, namely hormone synthesis and cell proliferation. It is clear that changes in ambient calcium concentration have a potent influence on PTH mRNA. Some, but not all, in vitro studies have suggested that while elevated calcium concentrations suppress PTH mRNA [7-9] the converse is not true. In vivo studies, which did not suffer from the progressive loss of calcium sensitivity that occurs in cultured parathyroid cells, have been more consistent and demonstrate quite convincingly that PTH mRNA is substantially increased by low calcium, with little or no influence of high calcium [10,11]. If correct, these findings suggest that the parathyroid cells have machinery well suited to adaptation to chronic calcium deficiency, with less well developed responses to the rarer environmental insult of calcium excess.

The possibility that parathyroid cell proliferation is regulated by ambient calcium concentration is controversial. Parathyroid cells grown in a low calcium medium manifest increased triitated thymidine uptake [12], although Naveh-Many and Silver [13], Wernerson et al. [14], and Svensson et al. [15] found little change in parathyroid cell proliferation rate in rats fed a low calcium diet, even though PTH gene transcription increased significantly.

**Disturbed calcitriol action and synthesis**

Calcitriol exerts several distinct but related actions on the parathyroids. The immediate effects of calcitriol on PTH secretion are subtle and uncertain. If present, these effects occur too rapidly to be the result of a genomic action of calcitriol, and would instead be the result of an action effected rapidly by intracellular messengers, or on the calcium sensor itself. Parathyroid cells possess specific high affinity receptors for calcitriol [16], as do other major target sites such as the intestine and bone. Radiolabelled calcitriol given systemically localizes in the nuclei of parathyroid cells [16] and parathyroid cells in culture manifest striking decreases of PTH mRNA content following exposure to calcitriol at concentrations that are physiologically relevant [17]. A decrease in gene transcription underlies the PTH message response to calcitriol [18]. In vivo the calcitriol effect on the PTH mRNA is maximal at 48 h, although it is detectable as early as 5 h.

The immediate consequences of parathyroid gene suppression by calcitriol are reduction of PTH synthesis (definite), reduction of parathyroid cell proliferation (definite) and somewhat less certain effects on parathyroid sensitivity to calcium and on the vitamin D receptor (VDR). Calcitriol is unusual in that it has the capacity to up-regulate its receptor, thereby amplifying its own action [19]. A number of studies have looked at the VDR in parathyroid tissue in uraemia and although early reports suggested that VDR expression in parathyroid cells was reduced in uraemia [20], some doubt has been cast on the results of these studies [21].

Enlarging glands become progressively more likely to develop nodular hyperplasia [22] and it is now clear that such glands are relatively resistant to the action of calcitriol. In parathyroid tissue manifesting nodular hyperplasia, the VDR is substantially diminished in the nodular areas [23] and the reduction in VDR expression and the resistance to the suppressive action of calcitriol in this tissue would provide further explanation for the failure of calcitriol to suppress PTH secretion in large glands [22].

As mentioned above, studies of parathyroid suppressibility by calcium have suggested pathological loss of suppressibility in the absence of calcitriol [6,24], and some studies have also shown that the suppressibility may be restored by administration of calcitriol [25, 26]. Many of the studies performed to examine this relationship have been of the high calcium/low calcium dialysis type as described above, and are subject to the same weaknesses [6].

In addition to a breakdown of the parathyroid cells' normal response to calcitriol (especially in areas of nodular hyperplasia), there are clear-cut and often profound disturbances to calcitriol synthesis [27]. Measurement of serum calcitriol in patients with various degrees of renal insufficiency shows a decreasing trend in parallel with decreasing GFR and progressive decreases in PTH [28]. Although calcitriol concentration in plasma may remain normal in many patients with mild and moderate renal insufficiency, there is little doubt that, when taken in the context of elevated circulating PTH in these individuals, calcitriol production is inappropriately low [28,29]. Studies by Ritz et al. have examined this issue further by assessing 'calcitriol reserve' in patients with mild renal insufficiency [30]. These subjects, in whom GFR averaged 70 ml/min, had normal baseline calcitriol concentration but, unlike the normal controls, were unable to mount an increment following the injection of pharmacological doses of PTH. Thus it appears that the PTH–calcitriol endocrine system was already maximally compensated, even at this relatively early stage in the progression of chronic renal insufficiency.

**Disturbed PTH action**

The most obvious site of this is the diseased kidney itself, which when damaged is increasingly unable to
increase its synthesis of calcitriol in response to PTH drive. The observed downward spiral of increasing parathyroid activity in the face of normal or near normal ECF calcium concentration is further exacerbated by PTH resistance in other potentially calcemic target tissues [31–35]. There is ample evidence indicating that skeletal responses to PTH are diminished in uraemia, and that part of this defect may be repaired by the replacement of deficient calcitriol [31,33,34]. Several studies have suggested in addition that an important part of the reduced calcemic response to PTH in uraemia is the result of phosphate retention [31,36]. Somerville and Kaye have shown that phosphate removal in acutely uraemic rats reinfused with their own urine restored the normal calcemic response to PTH [36].

Phosphate retention

The earlier work of Slatopolsky and Bricker in dogs with experimental renal insufficiency defined what appeared to be a central role of phosphate retention in the genesis of hyperparathyroidism [3]. These studies were carried out in the 1960s when calcitriol had not yet been identified and the mechanism of vitamin D resistance was unknown. The ‘trade off’ hypothesis that evolved largely from this work maintained that phosphate accumulation in uraemia exerted downward pressure on calcium with resulting secondary hyperparathyroidism [3,37]. Strong support for this view came from the observation that proportionate dietary phosphate restriction could attenuate or even prevent the development of hyperparathyroidism. The subsequent identification of calcitriol and the prompt realization that replacement of the deficient hormone in uraemic subjects could lead to marked suppression of PTH excess served to divert attention away from the role of phosphate, other than as an important contributor to extraosseous calcification. It is therefore of interest that a number of recent publications have looked again at the question of phosphate and its effect on the parathyroids [38–41 and reviewed in 37]. These studies have examined the possibility that phosphate itself exerts a direct action on the parathyroid cell, independent of any tendency for reciprocal changes in ECF calcium or of phosphate-induced inhibition of calcitriol synthesis. This notion was given substantial impetus by Lopez Hilker et al. who, by careful dietary manipulation in uraemic dogs, showed that reduction of dietary phosphate improved secondary hyperparathyroidism by a mechanism that was independent of either calcitriol or ECF calcium concentration [39].

Recently Combe and Aparicio examined the PTH–calcium relationship in patients with moderate renal insufficiency before and after dietary phosphate restriction [42]. Phosphate restriction led to reductions of basal PTH, PTHmax and PTHmin, but no change in the set point to calcium or in slope. Nevertheless there was clear evidence of a shift in the relationship between PTH and calcium, suggesting increased parathyroid suppressibility by calcium following dietary phosphate restriction. Very recent studies by Kilav et al. have now shown convincingly that, in rats with experimental renal insufficiency, dietary phosphate regulates parathyroid hormone—a low phosphate diet decreased and a high phosphate diet increased PTH mRNA levels indicating clearly that phosphate can now be added to the list of factors known to regulate parathyroid gene expression [43]. Whether or not phosphate directly influences parathyroid cell proliferation remains to be seen.

Metabolic acidosis

Metabolic acidosis, particularly when severe and sustained, has severe adverse consequences for the skeleton. Most clearly recognized are those that arise in the context of renal tubular acidosis, in association with which children manifest growth retardation and rickets and adults manifest osteomalacia. These skeletal lesions, although histologically similar to those of dietary vitamin D deficiency, are not in fact vitamin D dependent. Rather, they respond well to correction of the acidosis with alkali, usually without recourse to vitamin D therapy. Although chronic metabolic acidosis may under certain circumstances interfere with vitamin D metabolism [44], acidosis has not been shown to affect parathyroid function by this mechanism [45]. Recent reports have, however, pointed to a more direct influence of acidosis on parathyroid function. Two studies in particular have looked at this question [46 and Graham et al., personal communication], and although results are not in total agreement it now appears likely that rigorous correction of metabolic acidosis in haemodialysis patients may alter the relationship between calcium and PTH in a manner similar to that achieved by phosphate restriction [42]. Studies by Graham et al., as yet unpublished, have shown increased suppressibility of PTH by calcium following careful correction of uraemic acidosis. The mechanism of this effect is unknown and it is not known whether correction of acidosis affects only the parathyroid response to calcium, or whether acidosis is also a determinant of PTH gene expression, or even parathyroid cell proliferation.

Implications for clinical practice

As our understanding of factors that control the synthesis and secretion of PTH increases, so does the potential complexity of management strategies to deal with clinical parathyroid disorders in uraemia. The implications of the above discussion are that, if calcium, calcitriol, phosphate and acid–base status are set at appropriate levels, hyperparathyroidism and its sequelae should be avoidable. Although theoretically plausible, this strategy is rarely feasible in practice. Important confounding issues that arise include the inadequate or suboptimal nature of some of the therapies currently utilized (in particular those directed at
control of phosphate) and variable patient compliance. It is also apparent that there is considerable inter-patient variation in the propensity to develop hyperparathyroidism and that this variation goes beyond our understanding of known modulators. Finally there is the very important and as yet unresolved issue of defining the optimal PTH level in uraemia. Current thinking suggests that this is probably in the region of two to four times the upper limit of normal (100–200 pg/ml using an intact PTH 1-84 assay), but the evidence for this view is not robust. There is concern that suppression of PTH to levels below those given above may predispose patients to the development of adynamic bone disease. Conversely it is almost certain that under-suppression of PTH will allow accelerated parathyroid cell proliferation and the development of nodular hyperplasia. Indeed it is conceivable that, at least in some patients, the requirement for a sufficient degree of PTH excess to maintain normal bone turnover may inevitably allow the development of nodular hyperplasia. In other words, the needs of the skeleton and those of the parathyroid glands themselves may in some patients be in conflict to a degree that makes either adynamic bone disease or runaway hyperparathyroidism unavoidable. Such issues will be of increased importance with the emergence of non-calcemic vitamin D metabolites which may allow more targeted control of parathyroid function.

References

12. Roth SI, Raiz L. The course of reversibility of the calcium effect on the ultrastructure of the rat parathyroid gland in organ culture. Lab Invest 1966; 15: 1187–1211


