Molecular pathogenesis of secondary hyperparathyroidism in renal failure: basic and clinical aspects

M. Fukagawa and Y. Iwasaki

First Department of Internal Medicine, University of Tokyo School of Medicine and Division of Nephrology, Tokyo Teishin Hospital, Tokyo, Japan

Introduction

High turnover bone disease remains one of the central features of renal osteodystrophy seen in chronic dialysis patients [1]. This type of bone disease is caused by excess parathyroid hormone (PTH) secreted from markedly enlarged parathyroid glands [2]. Based on significant clinical and experimental observations, several models for the pathogenesis of secondary hyperparathyroidism in chronic renal failure have been proposed and new options of therapeutic modalities have recently become practical based on such models [3].

Resistance to calcitriol as a major mechanism of hyperparathyroidism in uraemia

Since decreased concentrations of ionized calcium and calcitriol stimulate PTH secretion, the treatment of hyperparathyroidism in chronic dialysis patients has been aimed mainly at ameliorating hypocalcaemia and at maintaining the physiological concentration of calcitriol [2,3]. Despite routine use of phosphate binders and oral active vitamin D sterols, it is still difficult to control PTH secretion in some patients. It has been reported that some of such patients may respond to supraphysiological concentrations of calcitriol achieved by calcitriol pulse therapy [4]. These observations suggest that the resistance of parathyroid cells to calcitriol may serve as another stimulus for PTH secretion in chronic renal failure [5].

Reduction of calcitriol receptor density in the parathyroid glands is currently considered to be the mechanism responsible for the resistance in chronic renal failure [6]. Although the precise mechanism is still controversial, disturbance in the upregulation of the calcitriol receptors by calcitriol itself [7] is considered to be the main mechanism leading to the decrease of calcitriol receptor density. Other mechanisms for the resistance to calcitriol include inhibited interaction of the calcitriol–receptor complex with target genes [8] and a recently revealed decrease of retinoid-X receptor density [9]. As renal failure progresses, this disturbance may form a vicious cycle of further reducing calcitriol receptor density leading to progressive resistance to calcitriol.

Parathyroid hyperplasia and resistance to calcitriol

Marked hyperplasia of parathyroid glands is a unique feature of hyperparathyroidism in chronic dialysis patients [10]. Long-term observation of patients treated by calcitriol pulse therapy revealed that the initial size of the parathyroid glands is the critical marker for the long-term prognosis of vitamin D therapy [11]. If at least one gland is larger than 1 cm in diameter or, more precisely, larger than 0.5 cm³ in volume, it is usually difficult to control PTH secretion in the long term. In such patients, hyperparathyroidism always relapses even if it initially responds to calcitriol pulse therapy. By contrast, patients with glands smaller than 0.5 cm³ respond to calcitriol pulse therapy well and can be controlled with active vitamin D sterols in the long term.

How can such differences in the response to calcitriol be explained? In patients with severe parathyroid hyperfunction, large parathyroid glands are usually composed of nodular hyperplasia, a more advanced type than the diffuse hyperplasia seen in small glands. Our data clearly show that the number of calcitriol receptors is decreased in nodular hyperplasia compared to diffuse hyperplasia [12]. Recently, we have demonstrated more direct evidence of parathyroid cell proliferation and the decrease of calcitriol receptor density [13]. Since nodular hyperplasia is demonstrated in more than 90% of glands heavier than 0.5 g [14], the difference in the response to calcitriol dependent upon gland size can be explained by these data.

Management of hyperparathyroidism in patients with parathyroid hyperplasia

In order to manage hyperparathyroidism in patients with marked parathyroid hyperplasia, we have
developed two new techniques in addition to calcitriol pulse therapy. The first technique is selective percutaneous ethanol injection (PEIT) [15]. We selectively destroyed the large glands resistant to calcitriol pulse therapy, thus leaving only small glands responsive to calcitriol [16]. After the successful destruction of large glands confirmed by Doppler ultrasonography, PTH secretion became controllable within the desired range using calcitriol therapy and conventional active vitamin D therapy, thus supporting our model. We have recently performed PEIT with a safer and more intensive protocol in which all glands larger than 0.5 cm³ are destroyed intensively within 1 week [17].

The second technique we have developed is direct calcitriol injection. Theoretically, higher concentrations of calcitriol should be more effective in suppressing the function of parathyroid glands with a lower density of calcitriol receptors, however, higher doses of calcitriol usually lead to marked hypercalcemia. To achieve very high concentrations of calcitriol locally within the parathyroid glands, we repeatedly injected calcitriol solution (1 µg/ml) directly into glands larger than 0.5 cm³ [18]. Direct calcitriol injections suppressed PTH hypersecretion and restored the responsiveness to calcitriol in chronic dialysis patients. Thus, a very high local concentration of calcitriol not only suppressed the function of parathyroid cells with a lower density of calcitriol receptors, but may also upregulate calcitriol receptor density in parathyroid cells.

Modulation of parathyroid cell function by gene transfer

We have also been trying to modulate abnormal parathyroid cell function by recently developed gene transfer techniques. For this purpose, we used the replication-deficient adenovirus vector because the adenovirus vector can transfer foreign genes very efficiently, irrespective of cell proliferation, both in vitro and in vivo. In our preliminary studies, PTH secretion became suppressed in response to very low concentrations of calcitriol by transferring functional genes into dispersed human parathyroid cells. Since we have also succeeded in transferring the lacZ gene into rat parathyroid glands by direct injection of virus solution, it will become possible to modulate parathyroid function in vivo by direct gene transfer using the adenovirus vector [19].

Conclusion

As shown in this review, parathyroid size can serve as useful marker for the selection of therapeutic modality for hyperparathyroidism in chronic dialysis patients. Cellular and molecular analyses of parathyroid hyperplasia have not only revealed new mechanisms underlying hyperparathyroidism, but have also greatly contributed to the development of new medical therapies.

References