Pathogenesis of refractory secondary hyperparathyroidism.

Calcitriol is currently used to reduce parathyroid hormone (PTH) levels in uremic patients. However, a significant number of patients fail to respond to calcitriol therapy. The data suggest that a poor response to calcitriol can be anticipated in patients with severe hyperparathyroidism (with a high basal PTH levels) and uncontrolled serum phosphate. The abnormal parathyroid response to calcitriol in uremic patients with severe parathyroid hyperplasia may be attributed, to a large extent, to the development of nodular hyperplasia as a result of clonal transformation from a diffuse polyclonal hyperplasia. The factors involved in the development of polyclonal parathyroid hyperplasia, at earlier stages of secondary hyperparathyroidism, appear to be the same factors that stimulate PTH secretion and synthesis: hypocalcemia, hyperphosphatemia and low serum calcitriol levels. Studies performed in vitro using parathyroid tissue from uremic patients who required parathyroidectomy demonstrate that in nodular hyperplasia there is an abnormal response to calcium and calcitriol, which suggests that there are factors intrinsic to the hyperplastic cell (such as decrease in calcium sensor receptor [8, 9]; also, the poor response to calcitriol treatment is associated with factors such as the failure to control the serum phosphorus [2, 10, 11]. This review will analyze the characteristics and factors involved in the pathogenesis of refractory hyperparathyroidism.

ABNORMAL PARATHYROID FUNCTION IN REFRACTORY HYPERPARATHYROIDISM

In a recent study [12] we analyzed parathyroid function (PTH-Ca curve) in 50 hemodialysis patients with PTH greater than 300 before and after 3 months of bolus calcitriol therapy (3–6 μg). Patients were divided into responders and non-responders based on whether the predialysis PTH value decreased by 40% or more in response to CTR treatment; this value was selected because it represented the median for the total group of 50 patients. Before initiation of treatment, the mean basal PTH, maximal PTH, and minimal PTH were greater in non-responders than responders. Serum calcium concentration was similar in both groups and the serum phosphate was greater in non-responders than responders. The data suggest that a poor response to calcitriol can be anticipated in patients with severe hyperparathyroidism and uncontrolled serum phosphate. The probability of a response to CTR based on pre-CTR basal PTH values is shown for the model in Figure 1. A 50% probability of a response (40% reduction in basal PTH) was observed at a pre-CTR basal PTH value of 750 pg/mL. At a basal PTH of 1200 pg/mL, the probability of a response to CTR was less than 20% and at a basal PTH of 400 pg/mL, the probability of a response approached 80%.

One of the parameters analyzed in this study was the ratio of basal to maximal PTH (basal PTH divided by the maximal PTH; this fraction was multiplied by 100), which in normal volunteers is 20% to 25% [13]. By correcting the actual PTH for the overall capacity to produce PTH (maximal PTH), a measure of the relative degree of PTH stimulation is obtained. When the basal calcium

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be attributed, to a large extent, to the development of nodular hyperplasia as a result of clonal transformation from a diffuse hyperplasia [15, 16]. Different research groups have reported that in nodular areas there is a decrease in calcium sensor receptor expression [8, 9], which may explain the abnormal response of these parathyroid glands to the increase in calcium induced by calcitriol administration. Calcitriol acts on parathyroid glands independently of calcium, however, the decrease in vitamin D receptor density also observed in nodular hyperplasia [7] may explain the refractoriness to calcitriol treatment. Studies performed in vitro using parathyroid tissue from uremic patients that required parathyroidectomy demonstrate that in nodular hyperplasia there is an abnormal response to calcium [17, 18] and calcitriol [19], which suggests that there are factors intrinsic to the cell (such as decrease in calcium sensor and vitamin D receptors) that are responsible for an abnormal regulation of parathyroid function. We have evaluated the ability of calcium to reduce PTH secretion in vitro in parathyroid tissue from uremic patients that required parathyroidectomy [18]. As shown in Figure 3, the degree of inhibition of PTH secretion by calcium was greater in diffuse than nodular hyperplasia; in primary parathyroid hyperplasia very high calcium concentrations were necessary to produce a significant decrease in PTH secretion. In a different study we evaluated in vitro, the effect of calcitriol on parathyroid cell cycle and apoptosis in parathyroid glands from patients with severe hyperparathyroidism [19]. In these glands, parathyroid cell proliferation was not inhibited by concentrations of calcitriol ranging from $10^{-10}$ to $10^{-8}$ mol/L; a moderate decrease in proliferation was observed when calcitriol concentration in the medium reached $10^{-7}$ mol/L (Fig. 4). In this study, it was observed that a high concentration of calcitriol produced a decrease in the number of apoptotic cells that was parallel to the decrease in proliferation. Because calcitriol simultaneously inhibits cell proliferation and apoptosis, a reduction in the parathyroid gland mass may not occur as a direct effect of calcitriol treatment.

**NODULAR HYPERPLASIA**

The reason for the high frequency of clonal proliferation is unclear. Probably the long-standing stimulation of a tissue with a usually extremely slow growth pattern favors clonal transformation; defects in DNA repair mechanisms may play a role [20]. Mendes et al [5] first described frequent nodular formations in parathyroid glands from uremic patients with severe secondary hyperparathyroidism. Nodular formation was observed in 50% of glands weighing between 0.25 and 0.5 g parathyroid and in more than 90% of glands weighing more than 0.5 g [21]. Nodules are formed by a greater proportion of

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**Fig. 1. Logistic regression model to predict response to calcitriol treatment.** Stepwise logistic regression analysis showed that the pre-calcitriol basal PTH level was the most important predictor of the probability of a 40% reduction in basal PTH during calcitriol treatment. Using the above model, a 50% probability of a response (40% reduction in basal PTH) was observed at a pre-calcitriol basal PTH value of 750 pg/mL. At a basal PTH of 1200 pg/mL, the probability of a response to calcitriol was less than 20%, and at a basal PTH of 400 pg/mL, the probability of a response approached 80%.
actively replicating cells [22–25]. Nodular hyperplasia was also associated with a greater resistance to medical suppression of PTH oversecretion [24, 25], and recurrence rates of hyperparathyroidism after PTX were significantly higher when nodular tissue instead of purely hyperplastic tissue was autografted [26].

Several authors have shown, using X chromosome inactivation analysis, that benign monoclonal tumors are present in a large proportion of hyperplastic glands [27–29] and there was no correlation between clonal development and morphology [27]. Clonal development may be caused by mutations or losses of tumor suppressor genes or activation of tumor enhancer genes [29, 30]. Losses on chromosome 11, the location of the *menin* gene, have been found in only 10% of the patients [31, 32] and allelic loss of the *Ha-ras* gene and the tumor suppressor gene *WT1* in approximately 10% of the patients [33]. The expression of calcium sensor receptor and vitamin D receptor are decreased in nodular hyperplasia, however, mutations of these two important receptors have not been identified [29].

**DIFFUSE HYPERPLASIA**

The nodular hyperplasia of the parathyroids occurs at a late stage in the evolution of secondary hyperparathyroidism. During earlier stages of secondary hyperparathyroidism, parathyroid growth is polyclonal. The factors
involved in the development of polyclonal parathyroid hyperplasia appear to be the same factors that stimulate PTH secretion and synthesis: hypocalcemia, hyperphosphatemia, and low serum calcitriol levels. The precise mechanism by which each of these factors stimulates parathyroid cell proliferation is unknown.

In rats on a low calcium diet with or without renal failure, there is a marked increase in parathyroid cell proliferation [34]. This effect is enhanced if rats have vitamin D deficiency. The importance of calcium on parathyroid cell growth in a clonal cell model has been proposed as a mediator of calcium-regulated parathyroid cell proliferation by increasing the expression of the cyclin-dependent kinase inhibitor p21, whereas a high phosphate diet may stimulate parathyroid cell proliferation by enhancing the expression of transforming growth factor-α (TGF-α).

There are genes potentially involved in uremic hyperparathyroidism. In uremic rats the increase in parathyroid cell proliferation is associated with increased c-myc expression [38]. Acidic fibroblast growth factor autocrine system has been proposed as a mediator of calcium-regulated parathyroid cell growth in a clonal cell model [54]. In hyperplastic human parathyroid glands, proliferating cells have a low expression of PTHrP [55] and an increased expression of TGF-α. [56]. Changes in the expression of all these genes may be the consequence rather than the cause of parathyroid hyperplasia.

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