Regression of parathyroid hyperplasia by calcimimetics—fact or illusion?

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Secondary hyperparathyroidism is one of the most common and serious complications of chronic kidney disease (CKD). The main factors responsible for excessive synthesis and secretion of parathyroid hormone (PTH) include phosphate retention, hypocalcaemia and calcitriol deficiency resulting from decreased kidney function [1,2]. Sustained hypersecretion of PTH is associated with an increase in the parathyroid gland size, initially leading to diffuse parathyroid hyperplasia. Subsequently, some cells in the parathyroid glands proliferate in a monoclonal growth pattern, and the enlarged glands exhibit an advanced type of nodular hyperplasia [3]. In the course of parathyroid hyperplasia, both calcium-sensing receptors (CaSR) and vitamin D receptors (VDR) are progressively down-regulated [4,5], which results in diminished responsiveness of parathyroid glands with nodular hyperplasia to active vitamin D treatment.

Conversely, whether regression of parathyroid hyperplasia can occur has remained a matter of discussion. Regression of parathyroid hyperplasia has been reported in rare cases of spontaneous infarction of the glands [6,7]. In addition, enhanced apoptosis of parathyroid cells has been observed in diffuse hyperplasia after kidney transplantation, suggesting the possibility of regression in the long term [8].

In the past, the capacity of calcitriol therapy to induce regression of parathyroid hyperplasia had been a matter of debate. In a study of oral calcitriol pulse therapy, given to chronic haemodialysis patients, we observed a significant decrease in the mean ± SD volume of parathyroid glands (from 0.87 ± 0.32 to 0.51 ± 0.23 cm³) after 12 weeks of treatment, with a concomitant significant reduction in intact PTH levels [9]. In contrast, Quarles et al. failed to observe a decrease in the parathyroid gland size after 36 weeks of intermittent intravenous or oral calcitriol treatments [10]; the mean ± SD gland volume was 1.9 ± 0.6 and 2.1 ± 0.7 cm³ before and 3.3 ± 0.8 and 2.3 ± 0.8 cm³ after oral and intravenous calcitriol therapy, respectively. The reduction in serum intact PTH observed in their study was relatively mild. The discrepancy between these two studies may be attributed to a more severe degree of hyperparathyroidism observed in the latter, as compared to the former study. We also reported that the long-term outcome after calcitriol pulse therapy was dependent on parathyroid change, and that patients with one or more glands >0.5 cm³ became refractory to calcitriol pulse therapy [11].

Taken together, these findings suggest that the degree of parathyroid hyperplasia can be an important determinant for regression in response to calcitriol therapy, and that 0.5 cm³ is approximately the critical size. This concept is supported by the histological analysis of surgically removed parathyroid glands, which revealed that most of the glands exceeding 0.5 g exhibited nodular formations [3]. Notably, regression of advanced nodular hyperplasia can be induced only by direct injection of calcitriol or its analogues into the glands [12].

In this context, the next question is whether the calcimimetic agent cinacalcet, which has become available only recently, is capable of inducing regression of parathyroid hyperplasia in CKD patients [13]. Calcimimetic agents allosterically increase the sensitivity of CaSR to extracellular calcium ions, thereby lowering PTH secretion [14,15]. Theoretically, if PTH hypersecretion is sufficiently suppressed by cinacalcet in the long term, regression of hyperplastic glands will be induced; however, little clinical data exist regarding the actual regression of parathyroid hyperplasia by cinacalcet treatment.

In this issue of the journal, Meola et al. report the effect of cinacalcet treatment on the size of hyperplastic parathyroid glands in haemodialysis patients [16]. Nine patients received 30–120 mg cinacalcet in conjunction with conventional treatment for 24–30 months. Serum intact PTH levels decreased significantly from 1196 ± 381 to 256 ± 160 pg/ml. In glands with a baseline volume <500 mm³, the mean ± SD volume of glands decreased significantly from 233 ± 115 to 102 ± 132 mm³. However, in glands with a baseline volume >500 mm³, the mean ± SD gland volume did not decrease (1036 ± 1062 versus 837 ± 1290 mm³). Interestingly, cystic degeneration and a decrease in vascular supply were also observed in several glands during cinacalcet treatment (Figure 1).
This study is the first to suggest that cinacalcet treatment may induce regression of parathyroid hyperplasia in CKD patients whose gland volume is not >0.5 cm³ at treatment initiation. In support of this finding, another case of parathyroid size regression in response to cinacalcet treatment has been recently reported [17]. Although these observations are promising, they need to be confirmed by studies in larger numbers of patients. Moreover, the precise mechanism involved in the reduction of the parathyroid gland size remains unclear.

Mizobuchi et al. recently demonstrated that high concentrations of calcimimetics induce apoptosis in parathyroid cells from uraemic rats in vitro [18]. In contrast, several investigators have failed to detect apoptosis in parathyroid cells in vivo [19,20]. Chin et al. demonstrated the possibility of regression of parathyroid hyperplasia, but the reduction in parathyroid volume was attributed to a decrease in cell volume but not in total cell number [21]. More recently, Lomonte et al. evaluated the oxyphil/chief cell ratio of glands excised from haemodialysis patients, suggesting that cinacalcet may, at least theoretically, induce apoptosis in chief cells of hyperplastic parathyroid glands [22]; however, whether the reduction in the parathyroid gland size reported by Meola et al. can be attributed to a decrease in the cell volume or number remains uncertain.

Calcimimetics have also been shown to upregulate CaSR and VDR expressions in uraemia [23,24]. These effects may facilitate the inhibitory effect of calcitriol or its analogues on PTH secretion and parathyroid cell proliferation, thereby leading to the reduction in the parathyroid gland size.

Meola et al. also reported a cystic degeneration of the parathyroid glands during cinacalcet treatment [16]. Such a morphologic change has never been previously reported. Further light microscopy analyses might help to determine whether the cystic degeneration by cinacalcet can be attributed to parathyroid cell apoptosis. The functionality of these cysts is also an important issue [25]. $^{99m}$Tc-MIBI scintigraphy may help to determine the presence of functioning parathyroid tissues within the cyst wall, since high MIBI uptake has been associated with proliferation of parathyroid cells [26].

Another interesting finding observed in this study was a reduction in the parathyroid gland vasculature during cinacalcet treatment [16]. High blood flow signals evaluated by power Doppler ultrasonography are associated with pathological features of nodular hyperplasia [27]. To date, however, there have been no reports showing a reduction in the parathyroid gland vasculature in CKD patients, except for rare cases associated with spontaneous infarction of the glands [6,7]. Conceptually, it is possible that the reduced vascularity observed in this study was secondary to enhanced apoptosis of parathyroid cells. Another possibility is that cinacalcet directly modulated the parathyroid blood flow through interaction with CaSR in the vasculature; however, effects of calcimimetic-mediated CaSR activation on specific vascular beds in the parathyroid gland have not been demonstrated thus far.

From a clinical point of view, it is important to identify the determinants of the efficacy of cinacalcet for secondary hyperparathyroidism. Cinacalcet has been shown to be efficacious in patients with severe parathyroid over-function [14] and recurrent secondary hyperparathyroidism due to parathyromatosis [28] and kidney graft recipients with persistent hyperparathyroidism [29], suggesting that cinacalcet is capable of controlling a severe type of hyperparathyroidism. However, there are not a few patients who develop severe hyperparathyroidism resistant to cinacalcet therapy and require parathyroidectomy [22]. A recent observational study also suggested that the long-term control of secondary hyperparathyroidism by cinacalcet is difficult in patients with enlarged parathyroid glands [30]. In this context, the finding by Meola et al. is of interest. They reported that significant reductions in parathyroid volume were observed only in glands with a baseline volume <500 mm³, suggesting that the pretreatment parathyroid size is a critical factor in the regression response produced by cinacalcet [16]. Such a possibility may be related to the resistance to long-term cinacalcet therapy in patients with nodular hyperplasia. Further studies are required to prove or disprove that cinacalcet induces regression of severe hyperparathyroidism associated with nodular hyperplasia.

It is also clinically important to clarify whether the reduced parathyroid gland size by cinacalcet therapy can be interpreted as reduced functionality of the gland. In the study of Meola et al., however, withdrawal of cinacalcet resulted in a rebound of intact PTH levels, even in those who had shown marked reduction in parathyroid volume [16]. This is in line with the fact that in kidney transplant recipients, interruption of cinacalcet has been shown to result in an immediate re-increase in serum PTH levels following its administration for 26 weeks [29]. Moreover, to the best of our knowledge, there are no clinical data showing that after long-term cinacalcet treatment the dose of the drug could be progressively reduced due to normalization of the parathyroid gland size. The clinical significance of the reduced parathyroid size by cinacalcet therapy should be examined by further clinical studies.

In conclusion, the demonstration by Meola et al., based on a study in small number of dialysis patients, that...
parathyroid gland volume can regress in response to cinacalcet treatment must still be considered as inconclusive. It clearly raises the question of the morphological changes induced in parathyroid tissue by this therapy. Larger studies should be conducted to confirm the reported promising effects and their clinical meaning in the treatment of CKD patients with secondary hyperparathyroidism.

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**References**


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