sepharose led to remission of proteinuria in selected patients. More remarkably, the chromatographic eluates caused proteinuria in rats, suggesting the existence of a circulating pathogenetic factor for changes in glomerular permselectivity. Despite all these observations, we cannot ascertain the linkage, if any, between proteinuria, hypoalbuminaemia and lipoprotein abnormalities. A putative nephrotic factor may explain these data. Intuitively, one may consider the presence of two or more nephrotic factors acting in cascade after being triggered by proteinuria, which may activate a signal transduction pathway that mediates cellular responses to increased protein synthesis. Hyperlipidaemia would be just a deleterious epiphenomenon.

Therefore, further studies are needed ...

The explanation of these extraordinarily complex phenomena, as the most remarkable icon of German science, Hermann von Helmholtz, taught us a century ago, will come from careful analysis of more comprehensible data. The available data, however, are not definitive and sometimes contradictory, making a new approach mandatory. We propose different research trends: (a) quantitative and qualitative studies of nephrotic proteinuria which have not been performed to date, in combination with (b) efforts in developing an in vitro assay, using hepatic cells, to test lipoprotein synthesis in response to the presence of candidate substances, and (c) turnover studies, assessing the response of protein production to changes in proteinuria and/or serum albumin concentration. Consequently, the use of stable isotope tracers is recommended since they may be injected repeatedly and a number of different proteins may be endogenously labelled in a single experiment.

**References**


**Resistence of parathyroid cell to calcitriol as a cause of parathyroid hyperfunction in chronic renal failure**

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**Key words:** calcitriol; phosphorus; hyperparathyroidism; parathyroid hyperplasia; chronic renal failure

**Introduction**

Control of secondary hyperparathyroidism is one of the major problems in the management of chronic dialysis patients [1]. It has long been believed that decreased ionized calcium and/or decreased production of calcitriol, both resulting from phosphorus retention, trigger PTH hypersecretion in chronic renal failure. Thus, the treatment of secondary hyperparathyroidism was aimed to minimize hypocalcaemia by dietary phosphorus restriction and by phosphate binders, and to maintain physiological concentration of calcitriol in circulation by the use of active vitamin D sterols. Nevertheless there have still been many dialysis patients with severe secondary hyperparathyroidism despite having their plasma calcium and calcitriol concentrations kept within normal range by appropriate therapy, suggesting that the resistance of parathyroid glands to calcitriol may play a role in the development of secondary hyperparathyroidism in chronic renal failure.

**Role of calcitriol in regulation of parathyroid function**

Recent advances in basic research have made it clear that calcitriol is the key regulator of parathyroid function. Calcitriol, as hypercalcaemia, directly suppresses PTH secretion and synthesis, and these effects...
are independent of hypercalcaemia. Calcitriol also modifies the set point of calcium for PTH secretion, possibly by modifying the function or synthesis of recently cloned calcium-sensing receptor or by other mechanisms. In addition to the regulation of PTH, calcitriol suppresses parathyroid cell proliferation, while hypercalcaemia has no such effect at least in the short term. Since large doses of calcitriol can induce the regression of parathyroid hyperplasia [1], calcitriol may not only suppress parathyroid cell proliferation but may also play a role in defining the overall cell turnover rate in the parathyroid gland and thus the parathyroid cell number, probably through balancing cell growth and death.

Thus in the normal condition, physiological concentration of calcitriol exerts its effect on parathyroid cells to properly balance the parathyroid function against several stimuli. Resistance of parathyroid cells to calcitriol can cause imbalance in this steady state, leading to parathyroid hyperfunction in chronic renal failure, i.e. PTH hypersecretion, hypersynthesis, and parathyroid hyperplasia [1].

**Resistance of parathyroid to calcitriol in chronic renal failure**

Introduction of calcitriol pulse therapy revealed that parathyroid glands of chronic dialysis patients are resistant to physiological concentration of calcitriol, but may be responsive to pharmacological concentration of calcitriol [2]. Such calcitriol pulse therapy, either intravenous or oral, can not only suppresses PTH secretion, but can also normalize the shifted set point for PTH secretion and can lead to the regression of parathyroid hyperplasia in chronic dialysis patients [1]. Thus it is quite certain that resistance of parathyroid cells to calcitriol plays an important role in the development of parathyroid hyperfunction in chronic dialysis patients.

In an animal model of mild chronic renal failure, PTH secretion, synthesis, and parathyroid cell proliferation were all enhanced despite the presence of normal plasma concentration of calcium and calcitriol [3]. Since such parathyroid hyperfunction returned to normal with pharmacological doses of calcitriol, resistance of parathyroid to physiological concentration of calcitriol is clearly present even from the early phase of chronic renal failure [3]. This may also be the case with patients in the early phase of chronic renal failure [1].

**Mechanism of resistance to calcitriol**

What mechanism is responsible for the resistance of parathyroid to calcitriol? It seems that the peak concentration of calcitriol is more important for the suppression of parathyroid hyperfunction than the total dose of calcitriol as shown in dialysis patients [2] and in experimental animals [4]. Reduction of calcitriol receptor density in parathyroid glands, first shown by Korkor [5], is compatible with such data and has been considered the central mechanism of the resistance to calcitriol.

Then what leads to the reduction of calcitriol receptor density in chronic renal failure? Calcitriol receptor is known to be up-regulated by calcitriol itself [6]. Thus disturbance of calcitriol receptor up-regulation by calcitriol can play a role in the reduction of calcitriol receptor number, leading to a vicious cycle of further resistance to calcitriol in chronic renal failure. In support of such a view there have been several reports suggesting impaired calcitriol receptor up-regulation in several organs in chronic renal failure, although the nature of disturbance, i.e. transcriptional, translational, or other level, is still controversial [7], as is its precise mechanism.

On the other hand calcitriol may not be the only regulator of calcitriol receptor. Russell and associates showed in the vitamin-D-depleted chick that dietary calcium can modulate calcitriol receptor mRNA level independent of calcitriol [8]. According to recent data, dietary phosphorus restriction ameliorates [9] or prevents [10] parathyroid hyperfunction in chronic renal failure independent of the changes in plasma calcium or calcitriol concentration. These data are in contrast to the classic roles of phosphorus restriction on parathyroid function through ameliorating hypocalcaemia or increasing calcitriol production by the kidney. Although there is no direct evidence yet, it is an attractive idea that phosphorus may modulate calcitriol receptor in parathyroid cells. If this is the case, dietary phosphorus restriction, one of the classic recommendations for secondary hyperparathyroidism in chronic renal failure, may revive as a state-of-the-art therapy, as protein restriction revived as a new therapy to prevent the progression of renal failure by alleviating glomerular hyperfiltration.

**Magnitude of parathyroid hyperplasia and resistance to calcitriol**

The magnitude of parathyroid hyperplasia also depends on the resistance to calcitriol. Our recent clinical study suggests that larger parathyroid glands are more resistant to calcitriol pulse therapy than smaller glands, both in terms of suppression of PTH hypersecretion and the regression of hyperplasia [11]. Histologically, larger parathyroid glands tend to show nodular hyperplasia rather than diffuse hyperplasia, which is usually seen in smaller glands. Available data suggest that nodular hyperplasia is a more progressed type of parathyroid hyperplasia than diffuse hyperplasia. Thus parathyroid cells in nodular hyperplasia have higher proliferative potential and higher recurrence rate after autotransplantation. Furthermore, shift of the set-point for PTH secretion is more severe in nodular hyperplasia than in diffuse hyperplasia.

Our recent study with surgically removed parathyroid glands clearly showed that calcitriol receptor
density was less in nodular hyperplasia than in diffuse hyperplasia, even in a same patient [12]. It was of note that a small nodule forming within diffuse hyperplasia showed much less density of calcitriol receptor compared with that of the surrounding tissue. Since calcitriol receptor density inversely correlated with gland weight, it is likely that larger glands represent nodular hyperplasia that has a lower density of calcitriol receptor and is thus more resistant to calcitriol. In other words, smaller glands may be still responsive to calcitriol in patients resistant to calcitriol pulse therapy. As an additional proof, we have recently shown that patients who were resistant to calcitriol pulse therapy became controllable by selectively deleting the largest gland(s), i.e. the most functioning and the most resistant cells to calcitriol, by ethanol injection [13].

At present, development of parathyroid hyperplasia in chronic renal failure can be summarized as a model below. In chronic renal failure, calcitriol receptor density in parathyroid cells decreases with phosphorus retention, and in its vicious cycle, parathyroid cells become resistant to calcitriol and begin to grow, leading to diffuse hyperplasia. Cells with a more severe decrease of calcitriol receptors then proliferate more vigorously to eventually form nodular hyperplasia. Monoclonal cell proliferation and gene rearrangement may occur later in some cells, probably within nodular hyperplasia as recently reported [14]. The mechanism of monoclonal cell growth and gene rearrangement remains to be clarified. In such patients, even calcitriol pulse therapy may not be effective any more.

Implications for the management strategy

Based on the thesis outlined above, we would like to propose both new and old principles in the management of parathyroid hyperfunction in chronic renal failure. The first principle is to begin treatment earlier since the resistance of parathyroid glands to calcitriol exists from the early phase of chronic renal failure. Thus early phosphorus restriction is most important and possibly with the use of active vitamin D [15] or even calcitriol pulse therapy before introduction of dialysis.

The second principle is to prevent the progression of parathyroid hyperplasia. This can be achieved by dietary phosphorus restriction, early use of calcitriol pulse therapy, and the routine evaluation of parathyroid size by ultrasonography as we have recently reported [11]. Once nodular hyperplasia is established, there will be no further indication of calcitriol pulse therapy since such patients will be resistant to calcitriol pulse therapy and often develop marked hypercalcaemia with the pulse therapy. Then how can we tell resistant parathyroid glands from responsive glands in advance of further therapy? Practically, size of parathyroid gland can serve as an index of resistance [11]. From our experience so far, long-term control of parathyroid hyperfunction by calcitriol pulse therapy is usually impossible in patients with enlarged parathyroid gland(s) larger than 1 cm in diameter. In such patients, reduction of functioning parathyroid tissue, which is most resistant to calcitriol, either by subtotal parathyroidectomy or selective ethanol injection into large gland(s) under ultrasonographic guidance [12] may restore the responsiveness to calcitriol pulse therapy.

In conclusion, we propose the resistance of parathyroid cells to calcitriol as an early event in the pathogenesis of secondary hyperparathyroidism in chronic renal failure. And we would like to stress the new roles of calcitriol and phosphorus in its management strategy. We should also remind ourselves of the importance of early prevention of parathyroid hyperfunction, especially prevention of markedly enlarged parathyroid hyperplasia in chronic renal failure.

Acknowledgements. This editorial comment was in part supported by grants from the Ministries of Education, Science and Culture and of Health and Welfare of Japan.

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