Ultrasonographic intervention of parathyroid hyperplasia in chronic dialysis patients: a theoretical approach

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Abstract. Calcitriol pulse therapy has markedly changed the management of secondary hyperparathyroidism in chronic dialysis patients. However, there are still many patients even resistant to this therapy. Our observation of parathyroid size by ultrasonography revealed that these patients usually have enlarged parathyroid glands larger than 0.5 cm³. Such large parathyroid glands are composed of nodular hyperplasia with monoclonal cell proliferation, whose calcitriol receptor density is lower than that of diffuse hyperplasia, thus more resistant to calcitriol. Based on such a pathophysiological model, we have shown that destruction of the largest parathyroid gland was sufficient to restore the responsiveness to calcitriol therapy in these refractory patients. By using colour Doppler ultrasonography, we could also optimize the site and volume of ethanol injection and could detect the recurrence of parathyroid cell growth easily, with lower risk of complications. This selective route of drug delivery to parathyroid glands can be also used for direct injections of calcitriol solution as we have reported. Thus, evaluation of parathyroid size by sensitive ultrasonography is an essential marker for the management of parathyroid hyperfunction in chronic dialysis patients. It is also suggested that ultrasonographic intervention of parathyroid hyperplasia may not only be a useful and safe adjunct to calcitriol pulse therapy, but may also serve as a new therapeutic modality for parathyroid diseases in future.

Key words: parathyroid hyperplasia; ultrasonography; ethanol injection; calcitriol

Introduction

Parathyroid hyperfunction is a major target of the management of bone diseases in chronic dialysis patients [1,2]. In addition to the development of intact parathyroid hormone (PTH) assay and other markers for bone metabolism, recent advancement has made ultrasonographic technology sensitive and compact enough for practical use for the assessment of parathyroid hyperplasia in these patients [3].

In this brief review, we first summarize the recent progress in the pathogenesis of parathyroid hyperfunction with an emphasis on parathyroid hyperplasia [4]. Then, based on such observations, we introduce interventional ultrasonography of parathyroid glands as a new tool for the better management of parathyroid hyperfunction in chronic dialysis patients.

Parathyroid size is a critical marker for the prognosis of vitamin D therapy

Marked hyperplasia of parathyroid glands is a unique feature of parathyroid hyperfunction in chronic dialysis patients [5]. The degree of hyperplasia is different in each patient and it even varies among the four glands in the same patient.

It has been demonstrated in chronic dialysis patients who have undergone parathyroidectomy that larger glands are seen in patients more refractory to medical therapy and that they have greater proliferative potential than smaller glands [6,7]. We have observed changes of parathyroid size during and after calcitriol pulse therapy and found that the size of the largest gland is a critical marker for the responsiveness to vitamin D therapy in chronic dialysis patients [8]. Thus, it is always difficult to control parathyroid hyperfunction in dialysis patients with at least one enlarged parathyroid gland greater than 0.5–1 cm maximum diameter or about 0.5 cm³ in volume. In such patients, enlarged glands never regress to normal size, and parathyroid hyperfunction always relapses even if it initially responds to calcitriol pulse therapy. This 'cut-off point' in gland size is in good agreement with surgical data in dialysis patients who have undergone subtotal parathyroidectomy in whom autoimplantation of tissue fragments from glands heavier than 0.5 g...
resulted in frequent relapse of parathyroid hyperfunction (Y. Tominaga, personal communication).

In sharp contrast to such patients, patients with smaller glands usually respond to calcitriol pulse therapy independent of the degree of PTH hypersecretion as assessed by plasma PTH, and can be controlled with active vitamin D sterols in the long term. Thus, assessment of parathyroid size is an important element for the decision-making of management strategy for parathyroid hyperfunction in chronic dialysis patients.

Role of calcitriol in the pathogenesis of parathyroid hyperplasia

What is the difference between large and small parathyroid glands in chronic dialysis patients? The fact that data on the regulation of parathyroid cell proliferation are scarce due to the lack of established parathyroid cell lines makes this question very difficult to answer satisfactorily [5].

It has been shown that larger glands are usually composed of nodular hyperplasia which is considered of a more advanced type than diffuse hyperplasia seen in smaller glands. Cells in nodular hyperplasia have more proliferative potential [6,7] and more abnormal regulation of PTH secretion than those in diffuse hyperplasia [9]. We have recently shown in dialysis patients that calcitriol receptor number is reduced more in nodular hyperplasia [10] than in diffuse hyperplasia [11]. Since calcitriol has been shown to suppress parathyroid cell proliferation [12,13], such difference in calcitriol receptor density may play a role in the development of parathyroid hyperplasia in chronic dialysis patients.

Furthermore, calcitriol receptor density was also inversely correlated with the weight of enlarged glands [11]. Thus, the difference in the response to vitamin D therapy which seems dependent upon gland size may be due, at least in part, to the difference of calcitriol receptor number in nodular (i.e. larger) and diffuse (i.e. smaller) hyperplastic parathyroid glands.

Progression of parathyroid hyperplasia

In chronic renal failure, even from its early phase, parathyroid cell growth is stimulated by several factors such as decreased plasma concentrations of ionized calcium and calcitriol. In addition, recent data suggest that phosphate retention may directly and indirectly stimulate parathyroid cell growth [14]. Along with these stimuli, calcitriol receptor density in parathyroid cells decreases, and calcitriol receptor up-regulation by calcitriol may be impaired at several steps, leading to a vicious cycle in calcitriol action in parathyroid cells [15,16] (Figure 1). Thus, parathyroid cells become resistant to calcitriol [17] and continue to grow, leading to diffuse hyperplasia.

Small nodules formed within diffuse hyperplasia tend to have a lower density of calcitriol receptors compared with the surrounding tissue [11]. Thus, cells with a more severe depletion of calcitriol receptors then proliferate more vigorously to eventually form nodular hyperplasia. Although monoclonal proliferation had been demonstrated only in highly advanced nodular hyperplasia [18], a recent report analysing individual nodules by Tominaga and associates demonstrated that all nodules were monoclonal and that each nodule may be of separate monoclonal origin [19]. In other words, whole nodular hyperplastic glands are composed of several monoclonal nodules, one of which may grow much more vigorously than others and may finally occupy the majority of the enlarged gland. Thus, monoclonal proliferation may not be the result [20], but rather the cause of nodular hyperplasia. The biochemical and molecular mechanisms responsible for the differences of proliferative potency among these nodules remain to be elucidated.

In a small number of patients, gene rearrangement may occur in some cells probably within nodular hyperplasia, leading to autonomous proliferation [21]. Such gene rearrangements in parathyroid glands in dialysis patients have not been analysed in sufficient depth to compare with those of primary hyperparathyroidism, such as PRAD1/cyclin D1 oncogene and multiple endocrine neoplasia type I (MEN-I) [22]. Analysis of gene rearrangements may reveal similar abnormalities in dialysis patients.

Destruction of parathyroid tissue by ethanol under ultrasonography

Obviously, prevention of parathyroid hyperplasia is the most desirable management, but what is the best treatment for patients with established marked parathyroid hyperplasia? Subtotal parathyroidectomy with autoimplantation of tissue fragments from the least proliferative gland may be the best treatment currently available [1,2]. In addition, direct ethanol injection
Ultrasoundography for parathyroid hyperplasia

into parathyroid glands has been gaining popularity as an alternative to surgery.

Percutaneous ethanol injection into parathyroid glands under ultrasonography was first introduced as a practical procedure by an Italian group [23,24] and there have been several case reports its success. We further improved this technique based on recent clinical and experimental observations and on the advancement of technology [25]. The principles of our improvement are demonstrated in our protocol shown in Figure 2.

The first principle is to destroy the smallest number of parathyroid glands necessary for the management of secondary hyperparathyroidism. This is important to avoid unnecessary parathyroid tissue destruction that may lead to adynamic bone disease due to relative hypoparathyroidism. Since larger glands are more resistant to calcitriol therapy than smaller glands, presumably due to more severe decrease of calcitriol receptors [11], we select the largest gland as the initial target for ethanol injection. Only when the destruction of the largest gland is not sufficient to control PTH hypersecretion do we destroy the next largest gland as shown in the flow chart (Figure 2).

The second principle is to optimize the site of ethanol injection. For this purpose, we have opted to use colour Doppler ultrasonography which can detect the tissue with ample blood supply due to marked proliferation. As shown in Figure 3, tissue destruction can be confirmed by the disappearance of blood flow. Furthermore, recurrence of parathyroid cell proliferation can be identified by the same technique.

The third principle is to avoid complications by ethanol leakage from injected glands, such as recurrent nerve palsy and fibrosis of surrounding tissue. Thus, we developed a new injection needle which has holes on its side [25]. In addition, the volume of ethanol to be injected should be about 70% of the calculated gland volume. The volume should be further decreased for glands larger than 1 cm in diameter, and the site for additional injections should be optimized by the help of Doppler ultrasonography.

The last principle is to continue proper vitamin D therapy and to watch for relapse after ethanol injection. Since it is assumed that the gland most resistant to calcitriol therapy has been destroyed, the control of parathyroid hyperfunction should be much easier either with calcitriol pulse therapy or with conventional oral active vitamin D therapy. However, excess suppression of parathyroid function should be avoided to prevent adynamic bone disease [26,27]. Thus, as suggested by some groups [28,29], serum intact PTH should be maintained between 150 and 200 pg/ml and serum alkaline phosphatase activity within the normal range.

Interventional ultrasonography as a new tool for the modification of parathyroid hyperfunction

With the progress of ultrasonography, direct injection can be a practical route of drug delivery to parathyroid glands. As we have preliminarily tested, direct injection of calcitriol solution into enlarged parathyroid glands suppressed PTH hypersecretion and restored the responsiveness to calcitriol in chronic dialysis patients [30]. These results may have been derived not only from the very high local concentration of calcitriol, but also from the up-regulation of calcitriol receptor. This direct route of administration of test agents may also be suitable for selective gene therapy of parathyroid glands in the future [31].

Genetic analysis of samples obtained by aspiration biopsy may be another possible example of practical interventional ultrasonography of parathyroid gland. Since some types of genetic abnormality can be detected by polymerase chain reaction, aspiration biopsy can be used for the source of DNA analysis. Such information will be very important for advancement of our understanding of the pathophysiology and biology of parathyroid hyperplasia and development of further therapy.

Prevention and management of parathyroid hyperplasia from early phase of chronic renal failure

Prevention of parathyroid hyperplasia should be one of the most important goals of the management strategy of renal osteodystrophy. This should be aimed at from the early phase of chronic renal failure prior to dialysis, when parathyroid hyperfunction is already seen in many patients. Mild dietary phosphorus restriction is the first step, with the subsequent use of phosphate binders as necessary. Early use of active vitamin D in pre-dialysis patients has been reviewed recently and recommended for the prevention of secondary hyperparathyroidism without adverse effects.
Parathyroid Hypofunction in Uremic Patients

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Of the Largest Gland or Parathyroidectomy

Ethanol injection into the largest gland can be an option for patients with severe hyperparathyroidism and responsiveness to active vitamin D therapy can be restored by this therapy. Further manipulation of parathyroid function by ultrasonography may become practical in the near future, improving patient management.

Concluding remarks

Our management strategy for parathyroid hyperfunction in chronic dialysis patients is summarized in Figure 4. As can be seen, selection of each therapeutic modality should be based on the degree of parathyroid hyperplasia. Ethanol injection into the largest gland can be an option for patients with severe hyperparathyroidism and responsiveness to active vitamin D therapy can be restored by this therapy. Further manipulation of parathyroid function by ultrasonography may become practical in the near future, improving patient management.

Acknowledgements

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References

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