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Original Article

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Intravenous calcitriol therapy in an early stage prevents parathyroid gland growth

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Abstract

Background. Both the phenotypic alterations of parathyroid (PT) cells, e.g. down-regulation of the calcium-sensing receptor, and the increase of the PT cell number in nodular hyperplasia are the main causes of refractory secondary hyperparathyroidism. It is of great importance to prevent PT growth in an early stage.

Methods. To examine a more effective method of calcitriol therapy for the prevention of PT hyperplasia, we randomized haemodialysis patients with mild hyperparathyroidism to receive either daily orally administered calcitriol ($n = 33$) or intravenous calcitriol ($n = 27$) over a 12-month study period. Calcitriol was modulated so as to keep the serum intact PTH level between 100 and 150 pg/ml.

Results. Both groups showed similar reductions of the serum PTH level and similar increases in serum calcium. In both groups, there were no significant changes in the serum phosphate level. Long-term daily oral calcitriol therapy failed to prevent the increase of both maximum PT volume and total volume, as assessed by ultrasonography; however, intravenous calcitriol therapy successfully suppressed this progression. In the daily, oral group, both the bone-specific alkaline phosphatase (BAP) and the *N*-telopeptide cross-linked of type I collagen (NTX) significantly decreased, which was probably due to the PTH suppression. However, these bone metabolism markers remained stable in the intravenous group. The total dosage of calcitriol during the study was comparable in both groups.

Conclusions. These data indicate that intravenous calcitriol therapy in an early stage of secondary hyperparathyroidism is necessary to prevent PT growth and to keep a good condition of bone metabolism.

Keywords: calcium; calcitriol; growth; parathyroid; phosphate

Introduction

Secondary hyperparathyroidism is a serious complication in patients with renal failure. It has been reported that its aetiological factors include active vitamin D (VD) deficiency, hypocalcaemia and an excessive level of phosphate (Pi). To treat this disorder, VD supplementation and the administration of a Pi binder have been performed. However, the correction of these serological abnormalities does not inhibit the excessive secretion of parathyroid hormone (PTH) in some patients. Concerning parathyroid (PT) hyperplasia in humans, diffuse hyperplasia may histologically deteriorate to nodular hyperplasia [1]. In the latter, quantitative (an increase in the cell count) and qualitative [a decrease in the expressions of vitamin D receptors (VDR) and calcium-sensing receptors (CaSR)] changes are marked, which may contribute to the medical therapy-refractory condition [2,3,4,5]. There is a secondary hyperparathyroidism-related increase in the PTH level when the value of creatinine clearance becomes 30 ml/min or less. Usually, the PTH level is controlled with oral VD preparations in the early stage. Even after dialysis is started, therapy with oral VD preparations is continued in many Japanese patients with an intact PTH level of ∼300 pg/ml or less, although there are slight differences among hospitals. When PTH control is difficult, this therapy is switched to intravenous (IV) VD therapy. However, the control of serum calcium (Ca) and Pi levels gradually becomes difficult, making the continuation of intravenous VD therapy difficult. On echography, PT enlargement suggests nodular hyperplasia, often requiring parathyroidectomy and percutaneous ethanol injection therapy. Briefly, it is important to inhibit deterioration to nodular hyperplasia for long-term control of secondary hyperparathyroidism.

With respect to VD administration methods, previous clinical studies compared oral-pulse/daily-oral treatment with IV treatment [6,7,8,9,10,11,12]. However, a consensus regarding VD-related changes in the PT volume has not been reached. Fukagawa *et al*. [13,14] reported a decrease in the PT volume on echography after VD pulse therapy for 12 weeks. Quarles *et al*. [6] indicated that there were no changes in the PT volume on echography nor magnetic

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resonance imaging (MRI) after intravenous VD therapy. In the former study, the PT volume was relatively small; therefore, intravenous VD therapy in the phase of diffuse hyperplasia, with a small PT volume, may inhibit PT enlargement. In an experiment using 5/6 nephrectomized rats, bolus VD therapy immediately after renal failure induction inhibited PT enlargement [15,16].

Considering that conventional daily oral (DO) VD therapy does not inhibit PT enlargement, we conducted a prospective randomized study to investigate the inhibitory effects of intravenous VD therapy in the initial phase of secondary hyperparathyroidism, in which PT enlargement begins, on PT enlargement.

Methods

Patient selection

A total of 77 patients were recruited into the study from 23 haemodialysis units from January 2004 to November 2005. Entry criteria included a serum intact PTH concentration between 100 pg/ml and 300 pg/ml, and three times weekly haemodialysis for >6 months. Patients were excluded for the following reasons: prior treatment with calcitriol oral pulse or IV calcitriol, corrected calcium exceeding 10.5 mg/dl, serum phosphorus >6.5 mg/dl or serum alkaline phosphatase <115 U/l.

Study protocol

The study protocol consisted of an initial 2-week control period and a 12-month treatment period. All patients signed informed consent forms prior to entering the study. During the control period, all vitamin D oral drugs and injections were discontinued for 2 weeks. A total of 77 patients were initially enrolled. Of these patients, five failed to complete the entry criteria. Seventy-two patients were randomized to receive one of the following two protocols: daily orally calcitriol (DO group) or IV calcitriol (IV group, Rocaltrol® Injection: KIRIN Brewery Ltd., Tokyo, Japan). IV calcitriol was administered three times weekly at the end of each dialysis treatment procedure. The planned duration of treatment was 12 months. A restricted randomization technique was employed to assign these study participants to the treatment groups. At registration, we employed the minimization method and assigned the subjects to two groups so that there were no differences in gender nor the presence or absence of previous VD therapy. Using this method, 72 patients were randomized to the DO ($N = 35$) and IV ($N = 37$) group.

Calcitriol was started at an initial dose of 0.25 μg in the DO group and 0.5 μg in the IV group, respectively. The dose of calcitriol was increased or decreased by 0.5 μg/week to maintain the serum PTH level between 100 pg/ml and 150 pg/ml. Upward adjustments of calcitriol doses were not performed if the serum calcium and phosphorus levels exceeded 10.5 mg/dl and 5.5mg/dl, respectively. Severe hypercalcaemia (serum calcium >11.5 mg/dl for 2 months), a low PTH level (intact PTH <100 pg/ml for 2 months) and low bone metabolism markers (when all bone metabolism markers were below the lower limits of the normal ranges for 2 months) were treated by discontinuing calcitriol. If the cessation of calcitriol was necessary, it was restarted with reference to the dose before discontinuation. As a rule, sevelamer hydrochloride was used as a phosphate-adsorbing agent to maintain serum phosphate levels ranging from 3.5 to 5.5 mg/dl. However, when control with sevelamer hydrochloride alone was difficult, the agent was combined with other phosphate-binding agents (calcium carbonate, etc.). As a rule, the dialysate Ca level was established as 3.0 mEq/l. Combination therapy with VD preparations other than the test agent, ipriflavone, bisphosphonate or aluminium preparations was contraindicated. Patients in whom a corrected Ca level of >10.5 mg/dl, a phosphate level of >6 mg/dl or a Ca/phosphate product of >65 mg^2/dl^2 had persisted for 4 weeks were excluded from this study.

Of the 72 patients who entered the treatment protocol, 60 completed the planned 12 months. Two subjects requested to end the involvement for unspecified personal reasons; one patient was removed from the study because of uncontrolled hypercalcaemia; three subjects were excluded due to the deterioration of other diseases. The remaining patients were excluded from this study due to a lack of data.

Biochemical parameters

During the study protocol, serum-corrected calcium and phosphorus were measured weekly. Serum intact PTH and alkaline phosphatase were determined monthly, and both bone-specific alkaline phosphatase (BAP) and *N*-telopeptide cross-linked of type 1 collagen (NTX) were measured at the start and in the 3rd, 6th and 12th month. Serum FGF23 levels were assessed at the outset of this study. Serum calcium and phosphorus were measured by each dialysis unit. Serum BAP was measured by Osteolinks BAP (Quidel Corpora Serum, San Diego, CA, USA). Intact PTH was measured by the Allegro Intact PTH kit; Nichols Institute Diagnostics, San Juan Capistrano, CA, USA. Serum osteocalcin (OC) was measured by Osteocalcin Test Kokusai-F (International Reagents Corporation, Tokyo, Japan). Concerning OC, the sale of a measuring kit was discontinued during the study period, and this parameter was excluded. Serum NTX was measured by OSTEOMARK® NTx serum (Inverness Medical Professional Diagnostics, Princeton, NJ, USA). Serum FGF23 was measured by the FGF-23 ELISA Kit (KAINOS LABORATORIES, INC., Tokyo, Japan).

Parathyroid gland imaging

At the start of the study protocol and after 12 months of therapy, patients in both treatment groups were scheduled for imaging studies to assess the PT gland size. Of the 60 patients, pre- and post-imaging studies were successfully performed in 58 patients. The PT gland size was assessed by ultrasonography before and after the treatment. Most of measurements of the PT gland size were made by the authors (M. Taniguchi and M. Tokumoto). Eleven of 58 patients were assessed by the medical laboratory technician in a distant institution. The measuring methods were

Table 1. Clinical features

	OD group	IV group	*P*-value
N	33	27	–
Age (years)	66 ± 10	59 ± 12	0.235
Gender (male/female)	19/14	17/10	0.438
Primary disease (DM/non-DM)	5/28	2/25	0.309
Haemodialysis duration (years)	7.5 ± 5.9	7.1 ± 6.7	0.867
History of vitamin D therapy (yes/no)	25/8	22/5	0.583
Dialysate calcium concentration (2.5/3.0 mEq/l)	2/31	7/20	0.065
Biochemical parameters at entry			
Corrected calcium (mg/dl)	9.2 ± 0.7	9.3 ± 0.7	0.915
Phosphate (mg/dl)	4.6 ± 1.0	5.0 ± 1.0	0.126
Alkaline phosphatase (U/l)	236 ± 94	227 ± 65	0.101
Intact PTH (pg/ml)	230 ± 100	282 ± 167	0.209
BAP (U/l)	30 ± 13	26 ± 13	0.154
OC (ng/ml)	23 ± 13	19 ± 12	0.265
NTX (nmol/l)	137 ± 87	146 ± 92	0.818
Parathyroid gland volume at entry			
Maximum gland (mm^3)	49 ± 73	96 ± 215	0.298
Total glands (mm^3)	65 ± 108	150 ± 292	0.169

Data are expressed as mean ± SD.
n, number of specimens; DM, diabetes mellitus; PTH, parathyroid hormone; BAP, bone-specific alkaline phosphatase; OC, osteocalcin; NTX, *N*-telopeptide cross-linked of type 1 collagen.

standardized as follows. The visualized glands were measured in the anterio-posterior (*a*), transverse (*b*) and longitudinal (*c*) dimensions to calculate PT volumes. We measured the PT size using the following formula:

Estimated PT volume $= \pi/6 \times a \times b \times c$.

Statistical analysis

Data are expressed as the mean ± SD. All statistical analyses were conducted using the DOCTOR SPSS II program (SPSS Japan Inc., Japan). We used the Mann–Whitney *U*-test for unpaired non-parametric data and the Wilcoxon signed-ranks test for continuous variables, as appropriate. Similar comparisons of PT gland volume before and after treatment values within groups were done using the Wilcoxon signed-ranks test. Logistic regression models were applied to identify the factors that significantly affect the prognosis of PT gland enlargement. A *P*-value <0.05 was considered significant.

Results

Clinical features

As shown in Table 1, both the DO group and the IV group were similar with regard to age, gender, primary disease, haemodialysis duration, history of vitamin D therapy and dialysate calcium concentration. Concerning haematological markers, we measured the levels of corrected calcium, phosphate, alkaline phosphatase (ALP), intact PTH, BAP, OC and *N*-telopeptide cross-linked of type I collagen (NTX). There were no significant differences between the two groups. As the sale of an OC-measuring kit was discontinued during the study period, OC was excluded from the subsequent survey.

Changes in biochemical parameters

After administration, the serum-corrected Ca levels significantly increased in the two groups (Figure 1A). There were no changes in the serum Pi level in both groups (Figure 1B). In the two groups, the intact PTH levels significantly decreased after 1 month (Figure 1C). There were no significant differences in any parameters between the two groups. The total doses of VD during treatment were 91.5 ± 40.6 μg and 82.9 ± 31.2 μg in the DO and IV groups, respectively, with no significant difference. There were no differences in the doses of Ca carbonate and sevelamer administration between the two groups. No patient took calcimimetics.

Parathyroid gland volume

There were no significant differences in the maximum PT gland volume at the start of administration nor total volume between the two groups (Table 1). We additionally evaluated the PT volume 12 months after the start of administration (Figure 2). In the DO group, the maximum PT gland volume significantly increased (49 ± 73 mm^3 → 101 ± 141 mm^3, $P = 0.007$). In the IV group, there were no changes in the volume (96 ± 215 mm^3 → 89 ± 170 mm^3). In the DO group, the total volume also increased (65 ± 108 mm^3 → 134 ± 196 mm^3, $P = 0.006$). In the IV group, there was no significant increase (150 ± 292 mm^3 → 135 ± 250 mm^3). There was a significant difference in the change of the PT volume between the two groups (Figure 3). The changes of both maximum and total gland volume were significantly larger in the DO group than those in the IV group ($P =$ 0.047 and 0.015, respectively).

Examination of factors influencing parathyroid gland enlargement

In this study, we investigated factors influencing PT gland enlargement using a logistic regression model. Initially, in our univariate logistic regression analysis, the serum-corrected Ca and ALP levels were detected as factors influencing PT gland enlargement, as shown in Table 2 ($P =$ 0.018 and 0.046, respectively). In particular, the odds ratio of corrected Ca was extremely high (3.028). Our multivariate analysis, in which the data were corrected with gender, primary disease, history of VD therapy and dialysate Ca concentrations, also showed that a higher serum-corrected Ca level at the start of administration promoted PT enlargement (Table 3). A study reported that FGF23 was a prognostic factor for refractory hyperparathyroidism [17]; therefore, we also reviewed this parameter. In our univariate analysis, the *P*-value of log FGF23 was 0.051, showing no significant difference. However, the number of patients was small, and we cannot rule out the possibility that FGF23 is a prognostic factor for PT enlargement.

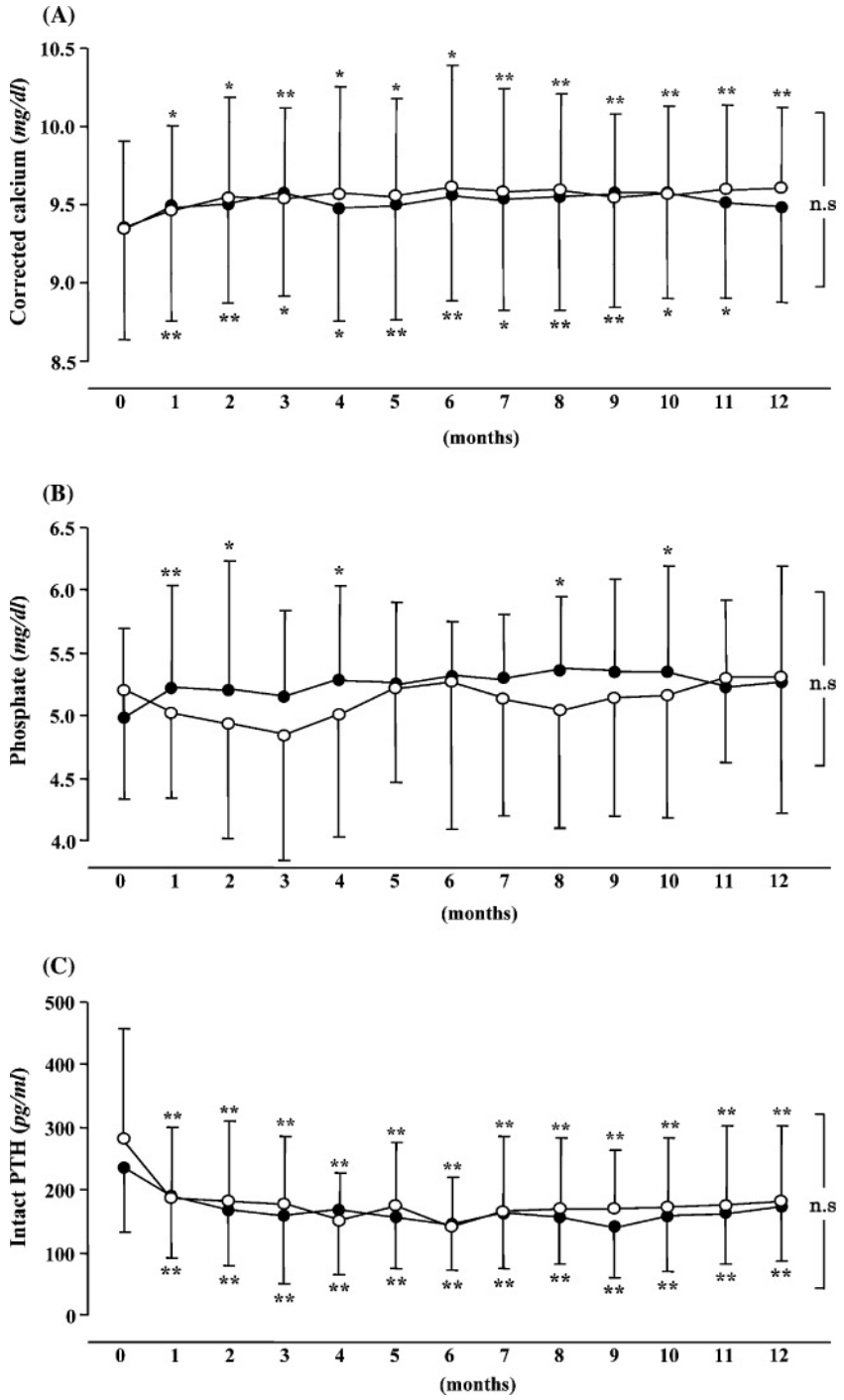

Fig. 1. Changes in serum biochemical parameters following treatment with daily oral and intravenous calcitriol for 12 months. **(A)** Effects of calcitriol therapy on serum-corrected calcium, **(B)** serum phosphate and **(C)** serum intact PTH concentrations. Calcitriol therapy was started at time zero. The daily oral (DO) group is represented by the closed circle (●), whereas the intravenous (IV) group is represented by the open circle (○). Data are expressed as mean ± SD. $^{*}P<0.05$, $^{**}P<0.01$ versus at time zero.

Changes in bone metabolism markers

Markers of bone metabolism were expressed as the rates of change in BAP and NTX (Figure 4). In the DO group, the BAP level significantly decreased 6 months or more after the start of administration. However, there were no changes in the IV group. In the DO group, the NTX level significantly decreased 3 months or more after the start of administration ($P<0.01$). In the IV group, it significantly decreased after 12 months or more ($P<0.05$). However, the decrease was less marked than that in the DO group.

Discussion

In this study, intravenous VD therapy in the early stage inhibited the deterioration of PT hyperplasia. There was no

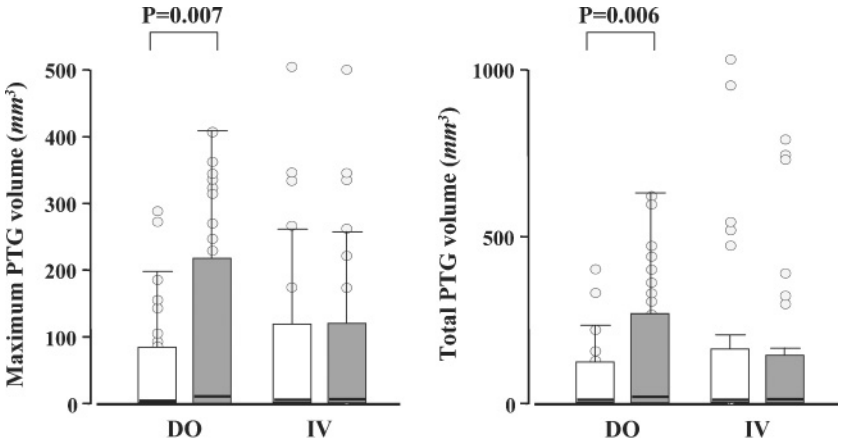

Fig. 2. Maximum and total parathyroid gland volume before (*white bar*) and after treatment (*grey bar*) with daily oral and intravenous calcitriol. DO, the daily oral group; IV, the intravenous group. Median values and interquartile ranges were given.

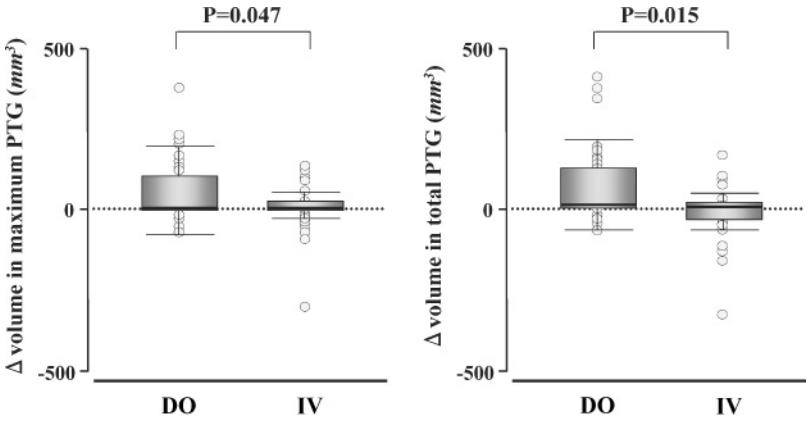

Fig. 3. Changes of maximum and total parathyroid gland volume during the treatment with daily oral and intravenous calcitriol. DO, the daily oral group; IV, the intravenous group. Median values and interquartile ranges were given.

significant difference in the total dose of calcitriol during the study period between the two groups; therefore, the difference in the administration method may have contributed to the inhibition of PT enlargement. These results suggest that intravenous VD therapy inhibits the deterioration from diffuse hyperplasia to nodular hyperplasia, a clinical problem. When the condition reaches nodular hyperplasia, its response to intravenous VD therapy is less marked due to quantitative (an increase in the cell count) and qualitative (decreases in the CaSR and VDR expressions) changes, requiring PT intervention in many cases. In our previous study regarding the PT gland after kidney transplantation, kidney transplantation did not cause quantitative nor qualitative changes in the nodular hyperplasia, but induced both quantitative (the enhancement of apoptosis) and qualitative (increases in the CaSR and VDR expressions) changes in the diffuse hyperplasia [18]. Briefly, these results suggest that intravenous VD therapy in the early stage maintains quality and quantity in diffuse hyperplasia, facilitating long-term conservative therapy. It may have any effect on the nodular hyperplasia qualitatively/quantitatively. An animal experiment showed that the bolus administration of VD in the early stage of renal failure inhibited PT hyperplasia, suppressing a decrease in VDR [15,19]. Furthermore, intravenous VD therapy may maintain the expression of CaSR, an aetiological factor for the medical treatment-refractory condition [20,21,22]. In another study that we performed, Ca/Pi control in patients with an intact PTH level of >300 pg/ml at the start of intravenous VD therapy was more difficult than in those with an intact PTH level of <300 pg/ml. It was also impossible to administer a sufficient dose of VD for a long period, requiring PT intervention in a high proportion of patients (data not shown). Poor Ca/Pi control may induce vascular calcification, leading to a poor prognosis. In contrast, the start of intravenous VD therapy in the phase of diffuse hyperplasia, in which the PTH level is low, may reduce the risk of PT intervention and achieve good Ca/Pi control, improving the prognosis.

In the present study, there were some important problems. Firstly, the target range of intact PTH level was comparably low. There was some risk of developing adynamic bone disease. In the K/DOQI guidelines [23], it is recommended that the intact PTH level in patients undergoing dialysis should be controlled to 150–300 pg/ml from the perspective of bone biopsy. When the intact PTH level exceeds 300 pg/ml, VD therapy, and if possible, intravenous VD

Table 2. Relative risk of parathyroid gland enlargement using univariate logistic regression models ($n = 60$)

	P-value	Odds ratio	95% confidence interval
Age (every 1 year)	0.840		
Gender (male/female)	0.266		
Primary disease (DM/non-DM)	0.301		
Haemodialysis duration (every 1 year)	0.224		
History of vitamin D therapy (yes/no)	0.380		
Dialysate calcium (2.5/3.0 mEq/l)	0.449		
Biochemical parameters at the start			
Corrected calcium (every 1 mg/dl)	0.018	3.028	1.214–7.552
Phosphate (every 1 mg/dl)	0.912		
Alkaline phosphatase (every 1 U/l)	0.046	0.991	0.982–1.000
Intact PTH (every 1 pg/ml)	0.351		
BAP (every 1 U/l)	0.185		
OC (every 1 ng/ml)	0.650		
NTX (every 1 nmol/l)	0.839		
FGF23 (every 1 ng/l)	0.116		
Log FGF23	0.051		

DM, diabetes mellitus; PTH, parathyroid hormone; BAP, bone-specific alkaline phosphatase; OC, osteocalcin; NTX, *N*-telopeptide cross-linked of type 1 collagen.

Table 3. Relative risk of parathyroid gland enlargement using multivariate logistic regression models ($n = 60$)

	P–value	Odds ratio	95% confidence interval
Corrected calcium (every 1 mg/dl)	0.017	3.662	1.260–10.644
Alkaline phosphatase (every 1 U/l)	0.043	0.987	0.975–1.000

Adjusted for gender, primary kidney disease, history of vitamin D therapy and dialysate calcium concentration.

therapy should be started. In Japan, the Japanese Society of Dialysis and Transplantation (JSDT) published guidelines on secondary hyperparathyroidism in 2006 [24]. It is recommended that the target intact PTH level should be established as 60–180 pg/ml with respect to the prognosis. In the adynamic bone disease, the reduced bone-buffer capacity would raise the serum levels of Ca and Pi, inducing vascular calcification. However, the present study revealed that both calcitriol therapies showed good Ca and Pi control (Ca $\times$ Pi product <55 mg^2/dl^2). This fact suggested that the target range of PTH level should be influenced by the prognosis. The second problem is the different effects to PT enlargement between daily, oral administration and IV administration. This finding was in agreement with previous studies [15], in which the prevention of PT enlargement in partial nephrecomized rat is more effectively suppressed when the same total dose of $1,25(OH)_2D_3$ is given by intermittent bolus administration than by continuous infusion. The high peak serum levels of $1,25(OH)_2D_3$ might be effective for preventing PT enlargement [25]; however, our study did not address this issue. The third problem is that the measurements of parathyroid gland size were made by some examiners in various centres. The accuracy of measurement might be unclear.

We investigated factors involved in PT enlargement using univariate and multivariate analyses. The results suggested the involvement of the serum Ca and ALP levels at registration. In particular, the former showed a high odds ratio. This may reflect a difference in the set point in the Ca–PTH relation curve. Briefly, the PTH level was high despite a high Ca level, suggesting that the condition had histologically reached nodular hyperplasia. Concerning the ALP level, the maintenance of the bone-buffer capacity may lead to a good Ca control. This may allow VD therapy at an increased dose, inhibiting PT enlargement. However, there was no such correlation with the BAP level; therefore, we cannot rule out the influence of liver dysfunction. Recently, Nakanishi *et al*. [17] reported that the blood FGF23 level was a prognostic factor for refractory hyperparathyroidism. However, in this study, there was no correlation between the blood FGF23 level and PT enlargement.

Previous studies have reviewed the actions of VD on bones. Many studies have reported that intravenous VD therapy relieved secondary hyperparathyroidism-related

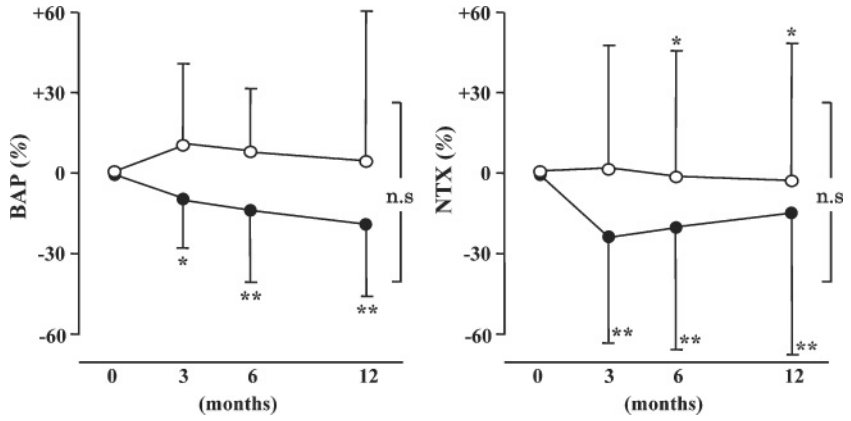

Fig. 4. Changes in serum biochemical parameters following treatment with daily oral and intravenous calcitriol for 12 months. Effects of calcitriol therapy on serum bone-specific alkaline phosphatase (BAP) and *N*-telopeptide cross-linked of type 1 collagen (NTX). Calcitriol therapy was started at time zero. Data are expressed as mean $\pm$ SD. $^*P < 0.05$, $^{**}P < 0.01$ versus at time zero.

osteitis fibrosa [26,27,28]. However, it remains to be clarified which of the two factors, the direct actions of VD or a decrease in the PTH level, is involved in the action mechanism. In this study, in the DO group, bone absorption and formation significantly reduced. In the IV group, the bone formation marker was comparably constant, with no decrease, in spite of a decrease in the PTH level. Several *in vitro* studies indicated that VD enhanced ALP activity directly [29,30,31,32]. These facts suggest that the difference of VD treatment method may affect bone metabolism *in vivo*. However, we could not explain the discrepancy between the effects on bone.

This study showed that intravenous VD therapy in the early stage significantly inhibited the deterioration of PT hyperplasia. Intravenous VD therapy in the phase of diffuse hyperplasia may prevent the deterioration to nodular hyperplasia, avoiding parathyroidectomy. In addition, good control of the serum levels of PTH, Ca and Pi may inhibit vascular calcification, improving the prognosis. When echography shows PT enlargement in the presence of mild secondary hyperparathyroidism, intravenous VD therapy should be started in the early stage.

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Conflict of interest statement. None declared.

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