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ORIGINAL ARTICLE

Reduction of whole PTH/intact PTH ratio as a predictor of bone metabolism in cinacalcet treatment of hemodialysis patients with secondary hyperparathyroidism

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Abstract
Summary In cinacalcet treatment of hemodialysis (HD) patients with secondary hyperparathyroidism (SHPT), not only intact parathyroid hormone (I-PTH), whole PTH (W-PTH), and bone markers, but also W-PTH/I-PTH ratio as proportion of active PTH(1–84) molecules were decreased. Changes in W-PTH/I-PTH ratio significantly correlated and predicted changes in bone marker.
Introduction Cinacalcet partly suppresses the secretion of PTH by enhancing PTH(1–84) degradation into N-truncated fragments. The objectives of this study is to investigate the significance of the N-truncated PTH/PTH(1–84) ratio for the prediction of the effect of cinacalcet in HD patients.
Methods Serum parameters were measured during 12 weeks of oral cinacalcet administration at 25 mg daily in 39 HD patients with SHPT.
Results Serum Ca, Pi, W-PTH, I-PTH, and W-PTH/I-PTH ratio all decreased significantly in a time-dependent manner during cinacalcet administration. Serum tartrate-resistant acid phosphatase (TRAP) 5b reflected these changes more precisely than serum N-telopeptide of type-I collagen. At 1 week, changes in I-PTH and W-PTH correlated significantly with those in serum Pi, but not Ca. Changes in serum Pi (but not Ca) and serum W-PTH also correlated significantly with changes in serum TRAP5b at both 4 and 12 weeks, while changes in serum I-PTH correlated significantly with those in serum TRAP5b only at 12 weeks. Changes in the serum W-PTH/I-PTH ratio correlated significantly with those in serum TRAP5b at both 4 and 12 weeks, and changes in serum W-PTH/I-PTH ratio at 4 weeks showed a tendency for a correlation with changes in serum TRAP5b at 12 weeks. HD patients with a reduced W-PTH/I-PTH ratio after 4 weeks had a significantly greater reduction of TRAP5b over 12 weeks.
Conclusion W-PTH and the W-PTH/I-PTH ratio allow estimation of the potency of cinacalcet in enhancement of PTH degradation, and thus no less reliable markers than I-PTH for reflecting cinacalcet-induced bone resorption.

Keywords Bone marker · Cinacalcet · Intact PTH · PTH(1–84) · PTH(7–84)-like fragment · Whole PTH

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Introduction

Cinacalcet is a calcimimetic that is an allosteric modulator of the calcium-sensing receptor (CaR), which is strongly expressed on the surface of parathyroid cells [1]. Cinacalcet enhances the sensitivity of the CaR to extracellular calcium, resulting in an increase in the intracellular calcium concentration and a concomitant reduction in parathyroid hormone (PTH) secretion from the parathyroid gland. In hemodialysis (HD) patients with secondary hyperparathyroidism (SHPT), cinacalcet reduces plasma PTH, serum phosphorus and calcium, and the calcium–phosphorus product [2–5]. Since an increase of serum Ca enhances PTH degradation from PTH(1–84) to PTH(7–84) in the parathyroid gland [6], it has also been proposed that cinacalcet enhances the PTH degradation step [7]. We have previously reported that the N-truncated PTH/PTH(1–84) ratio is negatively correlated

with serum Ca in HD patients [8] and in predialysis patients with chronic kidney disease (CKD) [9]. These data raise the possibility that serum levels of PTH might be overestimated when parathyroid activity is assessed by the intact PTH (I-PTH) assay, which has been demonstrated to be cross-reactive with biologically inactive N-truncated PTH molecules such as PTH(7–84), although a previous report suggested the lack of changes in N-truncated PTH/PTH(1–84) ratio during cinacalcet treatment [10]. Meanwhile, a whole PTH (W-PTH) assay has been newly developed to react specifically with biologically active full-length PTH(1–84), but not with biologically inactive N-truncated PTH molecules such as PTH(7–84). We have also shown that bone markers that are unaffected by accumulation in uremic serum due to renal impairment, such as serum tartrate-resistant acid phosphatase (TRAP) 5b, are superior to those that accumulate in uremic serum, such as serum N-telopeptide of type-I collagen (NTX) [11].

This background prompted us to examine which of the parathyroid markers W-PTH, I-PTH, and the W-PTH/I-PTH ratio best reflects the bone metabolic state during cinacalcet treatment over 12 weeks. The study was performed in a longitudinal manner with the further aim of showing the superiority of serum TRAP5b to serum NTX as a bone marker.

Patients and methods

Patients

A total of 39 uremic patients maintained on HD at Shirasagi Hospital and Nagayama Hospital (25 males and 14 females) were enrolled in the study after informed consent was obtained from each patient. The main entry criteria were mean I-PTH >300 pg/ml and albumin-corrected serum Ca> 9.0 mg/dl before treatment with cinacalcet. Patients with acute illness, significant infection or malignancy, and those who had received HD for <1 year were excluded; therefore, all the subjects were undergoing stable, regular HD using a bicarbonate dialysate. For 4 weeks before initiation of the study and 12 weeks during the study period, the regimen of drugs that could affect calcium metabolism, such as vitamin D derivatives and phosphate binders, was unchanged as far as possible. Due to adverse effects of cinacalcet such as fatigue, nausea, vomiting, depression and abdominal pain, or hypocalcemia, cinacalcet administration was withdrawn in two cases, and these patients were analyzed between the start and withdrawal of cinacalcet administration. The other 37 patients completed the study. The underlying kidney diseases were diabetic nephropathy (four patients) and nondiabetic nephropathy (35 patients). The study was approved by the Ethics Review Committee of Osaka City University Graduate School of Medicine.

Study design

Cinacalcet at a daily dose of 25 mg was taken orally once after dinner over a study period of 12 weeks. Blood was drawn in the morning after an overnight fast at 0, 1, 4, and 12 weeks. The specimens were kept on ice for 1 h and then centrifuged at 1,000×g for 10 min. The serum obtained was stored in aliquots at −20°C until assayed. The frozen samples were thawed and measurements were made immediately after thawing. Serum creatinine (Cr), albumin, Ca, Pi, and blood urea nitrogen were measured using an autoanalyzer. Serum Ca was expressed after correction for serum albumin level of 4.0 g/dl according to the following formula [12]: corrected Ca (mg/dl)={4.0−albumin (g/dl)}+Ca (mg/dl). Serum levels of $1,25(OH)_2D$ and 25(OH)D were measured using a radioimmunoassay [13].

Biochemical markers for calcium and bone metabolism

Biochemical markers for calcium and bone metabolism were measured as described previously [12, 14, 15]. Serum TRAP5b activity was measured by a novel fragment absorbed immunocapture enzymatic assay using two monoclonal antibodies [16]. Serum NTX was measured by ELISA (Osteomark NTX serum; Ostex International) [17, 18] with an intra-assay coefficient of variation (CV) of 4.6%. Serum bone alkaline phosphatase (BAP) was measured by enzyme immunoassay (ALKPHASE-B; Metra Biosystems) with an intra-assay CV of 2.2% [19].

PTH assay

Serum active PTH(1–84) was measured using a W-PTH assay (Scantibodies Laboratory, Inc., Santee, CA) using a two-site IRMA assay, as described previously [20]. Briefly, the W-PTH assay uses a polyclonal ^{125}I-labeled anti-PTH (1–84) antibody, which binds to the N-terminal region of the human PTH(1–84) molecule, and a capture antibody that recognizes the C-terminal region of PTH(1–84), which is fixed to the beads. According to the manufacturer's protocol, the antibodies exhibit no cross-reactivity against PTH(1–34), (2–34), (3–34), (4–34), (5–34), or (7–84) peptides [20–22]. The dose recovery was within 99.31–112.98% and the intra-assay and inter-assay CVs were 2.3–6.1% and 2.9–8.9%, respectively [20]. Serum I-PTH, which reflects both biologically active PTH(1–84) and the large C-terminal fragment that tends to accumulate in uremic patients [21, 23, 24], was measured by a second-generation Elecsys PTH electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany) [25, 26]. According to the manufacturer's protocol, the intra-assay and inter-assay CVs were 3.4–5.4% and 4.3–7.1%, respectively [26].

Statistical analysis

Data were analyzed using StatView 5.0J (Abacus Concepts, Inc.). Each result is expressed as a mean ± SD unless otherwise indicated. Correlation coefficients were calculated by simple regression analysis. Comparisons of changes in parameters were analyzed by Tukey–Kramer multiple comparison ANOVA test, with P values <0.05 considered statistically significant.

Results

Clinical characteristics of the HD patients

The baseline characteristics of the HD patients are shown in Table 1. The mean age (±SD) of the participants was 58.8± 11.5 years old. Two of the 39 secondary hyperparathyroidism (SHPT) patients were excluded from the study because of fatigue or nausea. The mean values of Ca, Pi, $1,25(OH)_2D$, and 25(OH)D were 10.0±0.6 mg/dl, 6.1±1.5 mg/dl, 7.3± 3.8 pg/ml, and 15.6±4.3 ng/ml, respectively, and the serum I-PTH and W-PTH levels were 733.8±384.4 and 348.4± 187.5 pg/ml, respectively. These values are significantly higher than the respective normal values of 42.1±16.4 and 25.9±10.9 pg/ml obtained in 346 and 127 Japanese healthy individuals, respectively [27, 28]. Consequently, the serum bone metabolic markers BAP, NTX, and TRAP5b were all significantly higher than their respective normal upper limits, with values of 47.5±53.2 U/L, 258.9±296.1 nmol bone collagen equivalent (BCE)/L, and 634.7±378.8 mU/dl, respectively, due probably to the development of SHPT.

Table 1 Baseline characteristics of the HD patients

Clinical variables	Number	Ranges
Age (years)	58.8±11.5	26.0–76.0
Male/female	25/14	
DM (+/−)	4/35	
HD duration (months)	22.0±30.1	2.4–145.0
Body height (cm)	160.2±10.3	142.0–183.5
Body weight (kg)	54.0±12.8	34.0–103.0
Ca (mg/dl)	10.0±0.6	8.4–11.0
Pi (mg/dl)	6.1±1.5	4.0–12.2
$1.25(OH)_2D$ (pg/ml)	7.3±3.8	0.0–16.1
25(OH)D (ng/ml)	15.6±4.3	6.0–24.0
I-PTH (pg/ml)	733.8±384.4	293.0–2,030.0
W-PTH (pg/ml)	348.4±187.5	98.3–1,050.0
BAP (U/L)	47.5±53.2	17.7–351.0
NTX (nmol BCE/L)	258.9±296.1	57.0–1,920.0
TRAP5b (mU/dl)	634.7±378.8	210.0–1,754.0

Data are expressed as mean ± SD

Time course of the effects of cinacalcet on PTH, Ca, and Pi metabolism

Time courses of the changes in serum Ca, Pi, and PTH during the 12-week study are shown in Fig. 1. W-PTH and I-PTH decreased significantly by 1 week after initiation of cinacalcet and then decreased in a time-dependent manner until week 12. Serum Ca and Pi also decreased significantly after week 1 and did not change significantly thereafter. The serum W-PTH/I-PTH ratio decreased in a time-dependent manner over the study period, with the reduction of this ratio first reaching a significant level after week 12.

Correlations between changes in I-PTH and W-PTH and those in serum Pi and Ca at 1 week after initiation of cinacalcet administration

At 1 week after initiation of cinacalcet, the changes in I-PTH were significantly positively correlated with those in serum Pi (r=0.622, p<0.0001), but not with those in Ca (r=0.090, p=0.5871; Fig. 2). Changes in W-PTH also showed a significant positive correlation with those in serum Pi (r=0.667, p<0.0001), but not with those in Ca (r=0.040, p=0.8106).

Effect of cinacalcet on bone metabolism

Serum TRAP5b and NTX, which are both bone resorption markers, had decreased significantly 1 week after initiation of cinacalcet and then decreased thereafter in a time-dependent manner (Fig. 3). Serum BAP, a bone formation marker, increased at weeks 1 and 4, although not significantly, and then decreased at week 12, suggesting cinacalcet-induced suppression of bone formation secondary to that of bone resorption via a coupling phenomenon. Among the bone resorption markers, serum TRAP5b, in contrast with serum NTX, decreased progressively in a time-dependent manner, supporting our previous reports of the superiority of serum TRAP5b as a marker in CKD patients [11, 29]. Therefore, we subsequently utilized serum TRAP5b as a bone marker reflecting cinacalcet-induced changes in bone metabolism.

Correlation of changes in serum Pi, but not in Ca, with those in serum TRAP5b

Changes in serum Pi showed a significant positive correlation with those in serum TRAP5b at both 4 and 12 weeks after initiation of cinacalcet (4 weeks: r=0.470, p=0.0025; 12 weeks: r=0.377, p=0.0234), in contrast with the lack of a significant correlation between changes in serum Ca and TRAP5b (4 weeks: r=0.194, p=0.2374; 12 weeks: r=0.084,

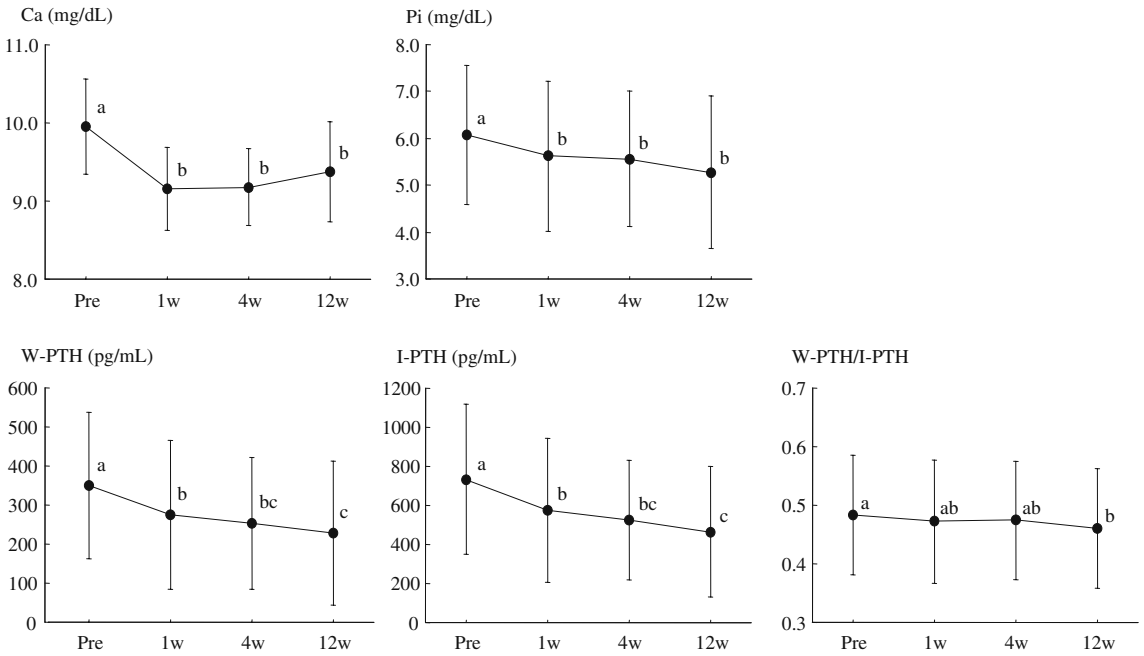

Fig. 1 Time courses of changes in serum Ca, Pi, and PTH during the 12-week study period. Serum Ca and Pi decreased significantly by 1 week and then did not change significantly thereafter. The serum W-PTH/I-PTH ratio decreased in a time-dependent manner over 12 weeks, and reduction of this ratio first reached statistical significance at 12 weeks. Values are presented as means ± SD. Significant differences ($p<0.05$) between means at each time point are indicated with different letters

$p=0.6258$; Fig. 4). Together with the correlation of changes in serum Pi, but not serum Ca, with those in serum PTH, these data suggest that the reduction of serum Pi might mainly be explained by decreased Pi release from bone caused by cinacalcet-suppressed PTH secretion from the parathyroid gland.

Correlations of changes in serum W-PTH and I-PTH with those in serum TRAP5b and the significance of the serum W-PTH/I-PTH ratio

Changes in serum W-PTH were significantly and positively correlated with those in serum TRAP5b at both 4 weeks ($r=$

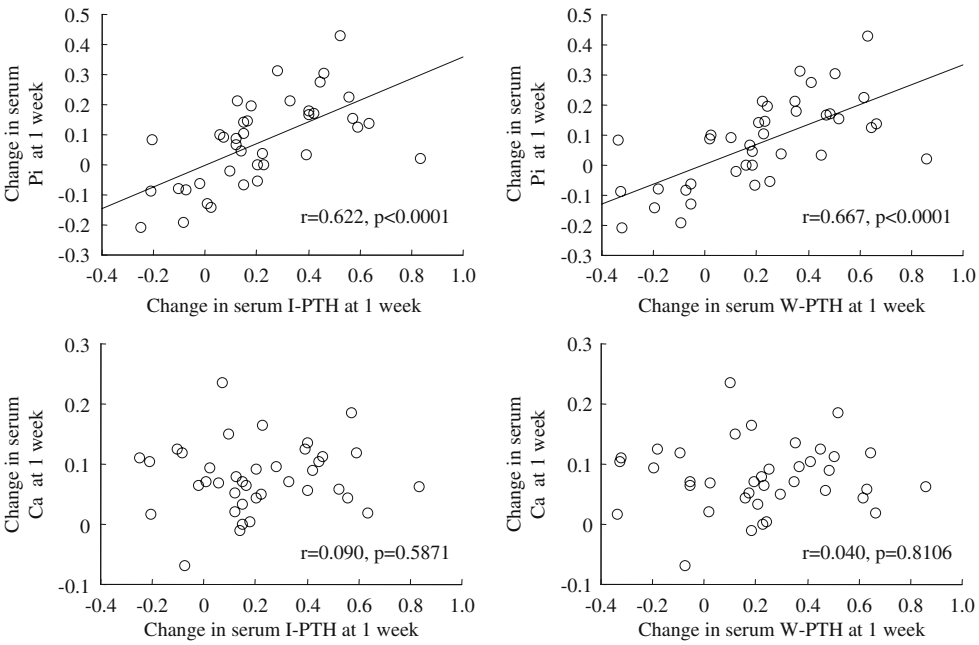

Fig. 2 Correlations between changes in I-PTH and W-PTH and those in serum Pi and Ca after 1 week. Changes in I-PTH correlated significantly in a positive manner with changes in serum Pi ($r=0.622$, $p<0.0001$), but with those in Ca ($r=0.090$, $p=0.5871$). Changes in W-PTH also showed a significant positive correlation with changes in serum Pi ($r=0.667$, $p<0.0001$), but not with those in Ca ($r=0.040$, $p=0.8106$). On each axis, a reduction is shown as a positive number and an increase as a negative number

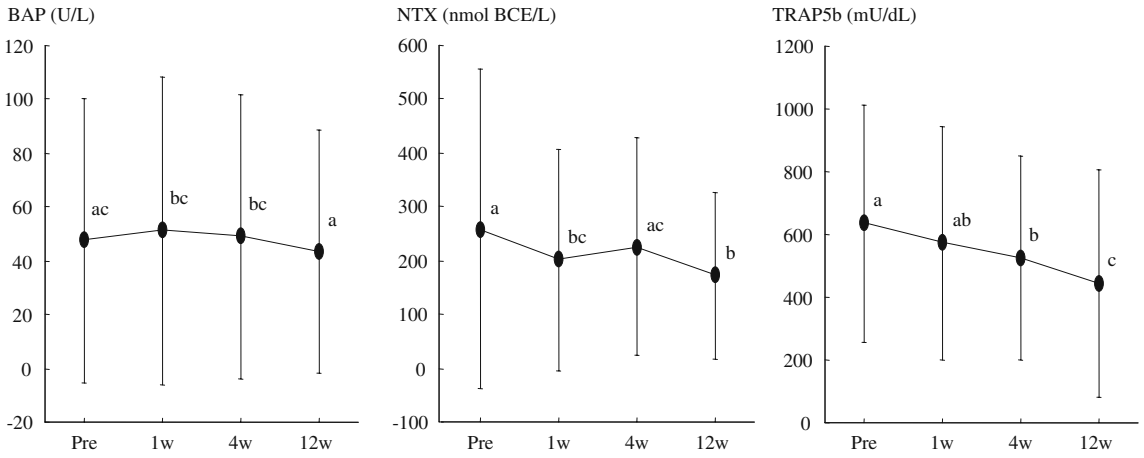

Fig. 3 Time courses of changes of serum bone markers during the 12-week study period. Serum TRAP5b and NTX, which are bone resorption markers, both decreased significantly by 1 week after initiation of cinacalcet and then decreased thereafter in a time-dependent manner. Serum BAP, a bone formation marker, increased after 1 and 4 weeks, but not significantly, and then decreased at 12 weeks. Values are presented as means ± SD. Significant differences ($p<0.05$) between means at each time point are indicated with different letters

0.358, $p=0.0252$) and 12 weeks ($r=0.574$, $p=0.0003$) after initiation of cinacalcet, whereas the correlation between changes in serum I-PTH and TRAP5b was significant at 12 weeks ($r=0.586$, $p=0.0002$), but not at 4 weeks ($r=0.298$, $p=0.0653$; Fig. 5). Of interest, the changes in the serum W-PTH/I-PTH ratio were significantly positively correlated with those in serum TRAP5b at both 4 weeks ($r=0.408$, $p=0.0099$) and 12 weeks ($r=0.342$, $p=0.0415$) after initiation of cinacalcet (Fig. 6). Furthermore, the changes in the serum W-PTH/I-PTH ratio after 4 weeks of cinacalcet treatment showed a tendency for a correlation with those in serum TRAP5b after 12 weeks ($r=0.279$, $p=0.0988$) of treatment.

Comparison of changes in serum bone resorption markers over 12 weeks in patients with and without reduction of the W-PTH/I-PTH ratio after 4 weeks

HD patients with a reduced W-PTH/I-PTH ratio at 4 weeks had a significantly greater reduction of TRAP5b at 12 weeks ($p=0.0314$) and a tendency for a greater reduction of NTX at 12 weeks ($p=0.0533$), compared with those without a

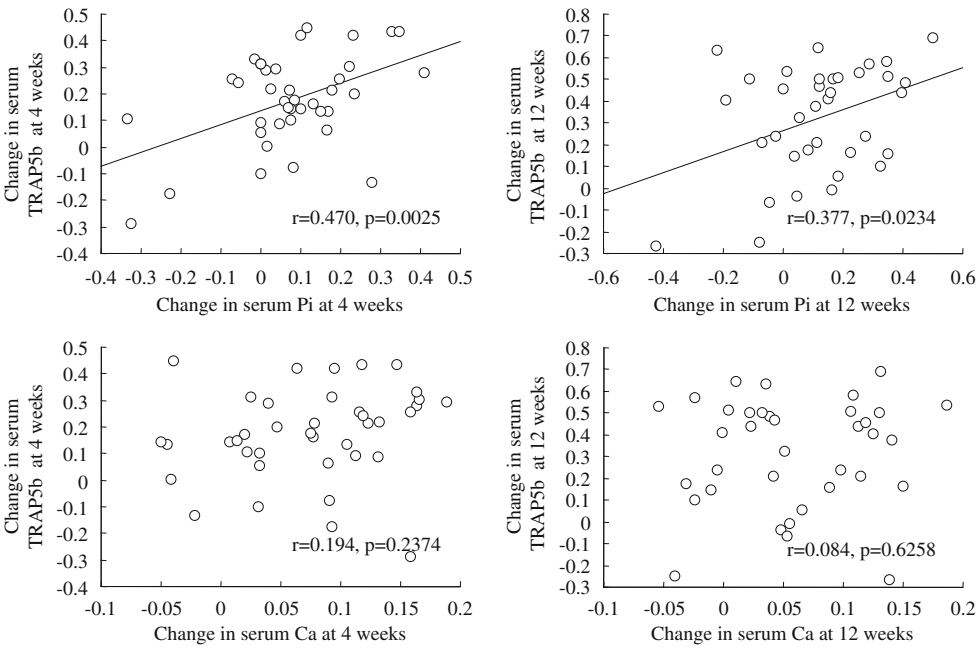

Fig. 4 Correlation of changes in serum Pi, but not Ca, with those in serum TRAP5b. The changes in serum Pi were significantly positively correlated with those in serum TRAP5b after 4 and 12 weeks of cinacalcet administration (4 weeks: $r=0.470$, $p=0.0025$; 12 weeks: $r=0.377$, $p=0.0234$). In contrast, there was no significant correlation between changes in serum Ca and TRAP5b (4 weeks: $r=0.194$, $p=0.2374$; 12 weeks: $r=0.084$, $p=0.6258$). On each axis, a reduction is shown as a positive number and an increase as a negative number

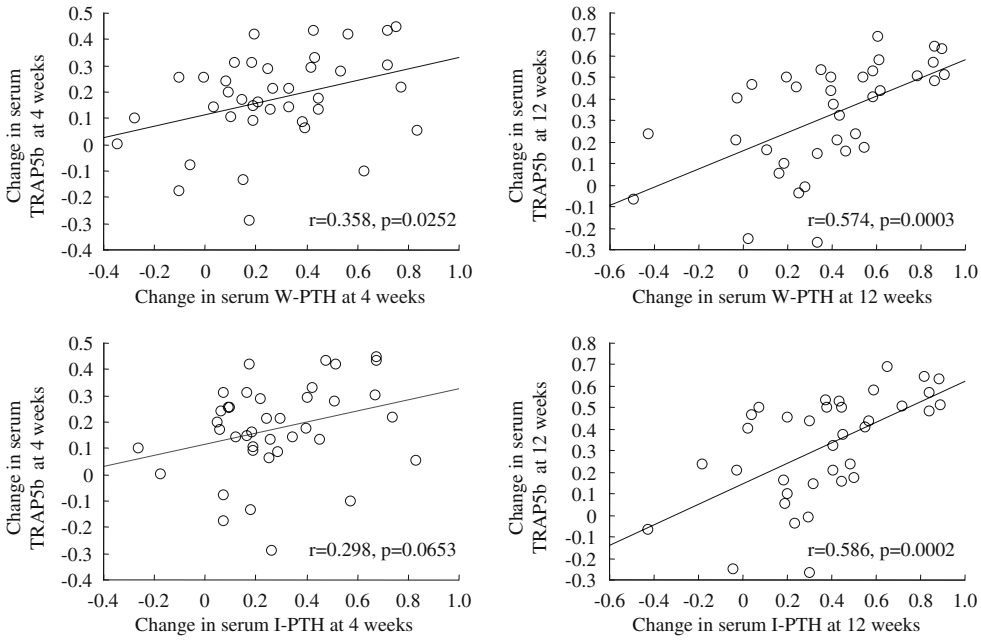

Fig. 5 Correlation of changes in serum W-PTH and I-PTH with those in serum TRAP5b. The changes in serum W-PTH were significantly positively correlated with those in serum TRAP5b at 4 weeks (r=0.358, p=0.0252) and 12 weeks (r=0.574, p=0.0003). The changes in serum I-PTH were correlated positively with those in serum TRAP5b at 4 weeks (r=0.298, p=0.0653, not significant) and 12 weeks (r=0.574, p=0.0003, significant). On each axis, a reduction is shown as a positive number and an increase as a negative number

reduced W-PTH/I-PTH ratio at 4 weeks. However, the difference in reduction of serum BAP did not differ significantly between the two groups (p=0.2161).

Discussion

The study showed that treatment with cinacalcet caused a reduction in serum W-PTH and I-PTH concomitantly with reduction of serum Pi and Ca in HD patients with SHPT. The suppressive effect of cinacalcet on parathyroid function was more precisely indicated by the change in serum W-PTH than those in I-PTH, as indicated by the stronger correlation of serum TRAP5b with serum W-PTH compared with serum I-PTH, and the finding that the change in the serum W-PTH/I-PTH ratio is a significant predictor of cinacalcet-induced suppression of bone resorption. Of interest, it seems that a change in serum Pi, but not serum Ca, after initiation of cinacalcet reflects a reduction in hydroxyapatite mobilized from the bone, as reflected by the significant correlation with the change in serum TRAP5b.

The W-PTH assay specifically recognizes the biologically active PTH(1–84) molecule, but not N-truncated PTH fragments such as PTH(7–84), whereas the second-

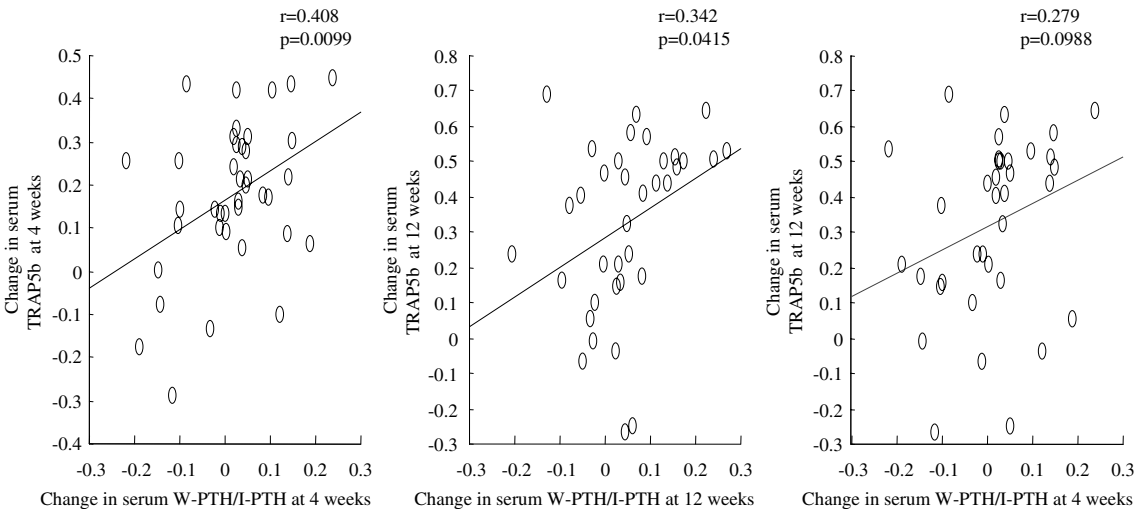

Fig. 6 Correlation of changes in the serum W-PTH/I-PTH ratio with those in serum TRAP5b. The changes in the serum W-PTH/I-PTH ratio were significantly positively correlated with those in serum TRAP5b at 4 weeks (r=0.408, p=0.0099) and 12 weeks (r=0.342, p=0.0415). The changes in the serum W-PTH/I-PTH ratio at 4 weeks showed a tendency for a correlation with those in serum TRAP5b at 12 weeks (r=0.279, p=0.0988). On each axis, a reduction is shown as a positive number and an increase as a negative number

generation I-PTH assay reacts with PTH(1–84), as well as with N-truncated PTH fragments, mainly PTH(7–84) [20–23]. In a primary-cultured parathyroid cell system, we showed that a decrease of Ca levels in culture medium prevented PTH degradation from PTH(1–84) to PTH(7–84) [6]. In an in vivo study of HD and predialysis CRF patients, we found that PTH(7–84) accumulates in uremic serum, probably through impaired excretion into urine due to renal dysfunction [8, 9], and that the proportion of active PTH molecules increases as the serum Ca levels decrease [8, 9]. Since PTH(1–84) is biologically active, in contrast with N-truncated PTH fragments such as PTH(7–84), serum W-PTH shows a no less significant correlation than serum I-PTH with serum TRAP5b. We have found that cinacalcet enhances PTH(1–84) degradation into N-truncated PTH molecules such as PTH(7–84) in primary-cultured parathyroid cells [7], which suggests that suppression of parathyroid activity by cinacalcet is reflected by reduction of the serum W-PTH/I-PTH ratio, in addition to cinacalcet-induced suppression of serum PTH. In fact, changes in the serum W-PTH/I-PTH ratio correlated significantly with changes in serum TRAP5b at both 4 and 12 weeks after initiation of cinacalcet. The most important finding in the study is that a reduction of the serum W-PTH/I-PTH ratio at 4 weeks may be a predictor of subsequent suppression of bone resorption by cinacalcet. A previous report suggested the lack of changes in N-truncated PTH/PTH(1–84) ratio during cinacalcet treatment [10] in which the authors did not mention when serum PTH had been measured after cinacalcet administration. The present study was designed to measure serum PTH immunoreactivities at 12 h after cinacalcet administration. Since we have observed a temporary 2–4 h suppression in serum W-PTH/I-PTH ratio after cinacalcet administration in the patients with PHPT (personal observation), the measurement of serum W-PTH/I-PTH ratio at 2–4 h after cinacalcet administration might be specifically important to predict the suppressive effect of cinacalcet on bone resorption.

It is of interest that changes in serum Pi in the current study correlated with those in serum W-PTH and I-PTH at 1 week after initiation of cinacalcet, in contrast with serum Ca, and that the changes in serum Pi correlated significantly with those in serum TRAP5b at 4 and 12 weeks. If the reduced levels of serum Ca and Pi are both due mainly to reduction of hydroxyapatite mobilization from bone by cinacalcet-induced PTH secretion, changes in serum Ca, in addition to those in serum Pi, should correlate significantly with bone markers. Since entry of Ca, but not Pi, through the intestine is strictly regulated by several mechanisms, it is possible that acute reduction of serum Ca could enhance Ca entry from the gut into the circulation. Alternatively, Pi is more widely distributed in the body, including in the intracellular space, and this may cause the equilibrium state of Pi to be more stable than that of serum Ca. Therefore, a reduction of hydroxyapatite degradation might be more precisely reflected by the change in serum Pi. These data suggest that a reduction in serum Pi at 4 weeks could serve as a predictor of a subsequent effect of cinacalcet on the parathyroid gland and on bone resorption.

Cinacalcet affects bone metabolism by suppressing parathyroid function. After cinacalcet administration, serum NTX and TRAP5b are decreased in a time-dependent manner, while serum BAP increases temporarily at 1 and 4 weeks and then decreases. The time course of the changes in bone markers was similar to those in our study of patients with uremic hyperparathyroidism after parathyroidectomy [30].

Time-dependent suppression of serum bone resorption markers indicated that cinacalcet inhibits PTH-induced bone resorption. Using bone histomorphometric analysis, we have shown that rapid elimination of PTH action by parathyroidectomy stimulates bone formation preferentially in cortical bone in patients with uremic hyperparathyroidism [31], and cinacalcet might have a similar strong effect on the suppression of parathyroid activity.

A limitation of the present study is that the serum parameters were measured approximately 12 h after cinacalcet was taken at a daily dose of 25 mg orally after dinner. The effect of cinacalcet on the PTH level disappears within 2–4 h in patients with PHPT [32], and there is probably a similar effect on the serum W-PTH/I-PTH ratio. Therefore, the significance of this ratio might be more apparent when serum parameters are measured shortly after cinacalcet administration. Furthermore, bone biopsy could provide a more precise analysis of the relationship with histomorphometric parameters in metabolically active cancellous bone, but this could not be performed due to its invasiveness.

Within these limitations, we conclude that W-PTH and the W-PTH/I-PTH ratio allow estimation of the potency of cinacalcet in enhancing PTH degradation and thus no less reliable markers than I-PTH for reflection of cinacalcet-induced bone resorption.

Conflicts of interest None.

References

1. Kawata T, Imanishi Y, Kobayashi K, Kenko T, Wada M, Ishimura E, Miki T, Nagano N, Inaba M, Arnold A, Nishizawa Y (2005) Relationship between parathyroid calcium-sensing receptor expression and potency of the calcimimetic, cinacalcet, in suppressing parathyroid hormone secretion in an in vivo murine model of primary hyperparathyroidism. Eur J Endocrinol 153:587–594
2. Block GA, Martin KJ, de Francisco AL, Turner SA, Avram MM, Suranyi MG, Hercz G, Cunningham J, Abu-Alfa AK, Messa P,

Coyne DW, Locatelli F, Cohen RM, Evenepoel P, Moe SM, Fournier A, Braun J, McCary LC, Zani VJ, Olson KA, Drueke TB, Goodman WG (2004) Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med 350:1516–1525
3. Moe SM, Cunningham J, Bommer J, Adler S, Rosansky SJ, Urena-Torres P, Albizem MB, Guo MD, Zani VJ, Goodman WG, Sprague SM (2005) Long-term treatment of secondary hyperparathyroidism with the calcimimetic cinacalcet HCl. Nephrol Dial Transplant 20:2186–2193
4. Messa P, Macario F, Yaqoob M, Bouman K, Braun J, von Albertini B, Brink H, Maduell F, Graf H, Frazao JM, Bos WJ, Torregrosa V, Saha H, Reichel H, Wilkie M, Zani VJ, Molemans B, Carter D, Locatelli F (2008) The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. Clin J Am Soc Nephrol 3:36–45
5. Lindberg JS, Culleton B, Wong G, Borah MF, Clark RV, Shapiro WB, Roger SD, Husserl FE, Klassen PS, Guo MD, Albizem MB, Coburn JW (2005) Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. J Am Soc Nephrol 16:800–807
6. Kawata T, Imanishi Y, Kobayashi K, Onoda N, Takemoto Y, Tahara H, Okuno S, Ishimura E, Miki T, Ishikawa T, Inaba M, Nishizawa Y (2005) Direct in vitro evidence of extracellular Ca2+-induced amino-terminal truncation of human parathyroid hormone (1–84) by human parathyroid cells. J Clin Endocrinol Metab 90:5774–5778
7. Imanishi Y, Kawata T, Kobayashi K, Wada M, Onoda N, Takemoto Y, Okuno S, Tahara H, Ishimura E, Ishikawa T, Nagano N, Miki T, Inaba M, Nishizawa Y (2007) Stimulation of calcium-sensing receptor truncate human (1–84) parathyroid hormone amino-terminally in vitro by human parathyroid cells. J Am Soc Nephrol 18(Abstract Issue):753A (Abstract no. SU-PO764)
8. Inaba M, Okuno S, Imanishi Y, Ueda M, Yamakawa T, Ishimura E, Nishizawa Y (2005) Significance of bio-intact PTH(1–84) assay in hemodialysis patients. Osteoporos Int 16:517–525
9. Kurajoh M, Inaba M, Yamada S, Imanishi Y, Tsuchida T, Ishimura E, Nishizawa Y (2008) Association of increased active PTH(1–84) fraction with decreased GFR and serum Ca in predialysis CRF patients: modulation by serum 25-OH-D. Osteoporos Int 19:709–716
10. Martin KJ, Juppner H, Sherrard DJ, Goodman WG, Kaplan MR, Nassar G, Campbell P, Curzi M, Charytan C, McCary LC, Guo MD, Turner SA, Bushinsky DA (2005) First- and second-generation immunometric PTH assays during treatment of hyperparathyroidism with cinacalcet HCl. Kidney Int 68:1236–1243
11. Shidara K, Inaba M, Okuno S, Yamada S, Kumeda Y, Imanishi Y, Yamakawa T, Ishimura E, Nishizawa Y (2008) Serum levels of TRAP5b, a new bone resorption marker unaffected by renal dysfunction, as a useful marker of cortical bone loss in hemodialysis patients. Calcif Tissue Int 82:278–287
12. Inaba M, Terada M, Nishizawa Y, Shioi A, Ishimura E, Otani S, Morii H (1999) Protective effect of an aldose reductase inhibitor against bone loss in galactose-fed rats: possible involvement of the polyol pathway in bone metabolism. Metabolism 48:904–909
13. Ishimura E, Nishizawa Y, Inaba M, Matsumoto N, Emoto M, Kawagishi T, Shoji S, Okuno S, Kim M, Miki T, Morii H (1999) Serum levels of 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, and 25-hydroxyvitamin D in nondialyzed patients with chronic renal failure. Kidney Int 55:1019–1027
14. Inaba M, Nishizawa Y, Mita K, Kumeda Y, Emoto M, Kawagishi T, Ishimura E, Nakatsuka K, Shioi A, Morii H (1999) Poor glycemic control impairs the response of biochemical parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in patients with type 2 diabetes. Osteoporos Int 9:525–531
15. Kumeda Y, Inaba M, Tahara H, Kurioka Y, Ishikawa T, Morii H, Nishizawa Y (2000) Persistent increase in bone turnover in Graves' patients with subclinical hyperthyroidism. J Clin Endocrinol Metab 85:4157–4161
16. Ohashi T, Igarashi Y, Mochizuki Y, Miura T, Inaba N, Katayama K, Tomonaga T, Nomura F (2007) Development of a novel fragments absorbed immunocapture enzyme assay system for tartrate-resistant acid phosphatase 5b. Clin Chim Acta 376:205–212
17. Gertz BJ, Clemens JD, Holland SD, Yuan W, Greenspan S (1998) Application of a new serum assay for type I collagen cross-linked N-telopeptides: assessment of diurnal changes in bone turnover with and without alendronate treatment. Calcif Tissue Int 63:102–106
18. Clemens JD, Herrick MV, Singer FR, Eyre DR (1997) Evidence that serum NTx (collagen-type I N-telopeptides) can act as an immunochemical marker of bone resorption. Clin Chem 43:2058–2063
19. Gomez B Jr, Ardakani S, Ju J, Jenkins D, Cerelli MJ, Daniloff GY, Kung VT (1995) Monoclonal antibody assay for measuring bone-specific alkaline phosphatase activity in serum. Clin Chem 41:1560–1566
20. Gao P, Scheibel S, D'Amour P, John MR, Rao SD, Schmidt-Gayk H, Cantor TL (2001) Development of a novel immunoradiometric assay exclusively for biologically active whole parathyroid hormone 1–84: implications for improvement of accurate assessment of parathyroid function. J Bone Miner Res 16:605–614
21. John MR, Goodman WG, Gao P, Cantor TL, Salusky IB, Juppner H (1999) A novel immunoradiometric assay detects full-length human PTH but not amino-terminally truncated fragments: implications for PTH measurements in renal failure. J Clin Endocrinol Metab 84:4287–4290
22. Souberbielle JC, Boutten A, Carlier MC, Chevenne D, Coumaros G, Lawson-Body E, Massart C, Monge M, Myara J, Parent X, Plouvier E, Houillier P (2006) Inter-method variability in PTH measurement: implication for the care of CKD patients. Kidney Int 70:345–350
23. Lepage R, Roy L, Brossard JH, Rousseau L, Dorais C, Lazure C, D'Amour P (1998) A non-(1–84) circulating parathyroid hormone (PTH) fragment interferes significantly with intact PTH commercial assay measurements in uremic samples. Clin Chem 44:805–809
24. Inaba M, Nakatsuka K, Imanishi Y, Watanabe M, Mamiya Y, Ishimura E, Nishizawa Y (2004) Technical and clinical characterization of the Bio-PTH (1–84) immunochemiluminometric assay and comparison with a second-generation assay for parathyroid hormone. Clin Chem 50:385–390
25. Reichel H, Esser A, Roth HJ, Schmidt-Gayk H (2003) Influence of PTH assay methodology on differential diagnosis of renal bone disease. Nephrol Dial Transplant 18:759–768
26. Roth HJ (2000) Elecsys parathyroid hormone (PTH) not detecting the large PTH fragment hPTH (7–84)? Clin Lab 46:295–299
27. Hiroyuki Y, Motomiya Y, Uchida K, Akizawa T (2002) Development and clinical application of whole PTH (PTH1–84) kit. Jpn J Med Pharm Sci 48:243–247
28. Inomata K, Yamashita H, Yamamoto A, Yukishita M, Adachi M (2004) Influence of 25-hydroxyvitamin D concentration on the reference range of intact PTH. Osteoporosis Jpn 12:449–456
29. Yamada S, Inaba M, Kurajoh M, Shidara K, Imanishi Y, Ishimura E, Nishizawa Y (2008) Utility of serum tartrate-resistant acid phosphatase (TRACP5b) as a bone resorption marker in patients with chronic kidney disease: independence from renal dysfunction. Clin Endocrinol 69:189–196
30. Yajima A, Inaba M, Ogawa Y, Tominaga Y, Tanizawa T, Inou T, Otsubo O (2007) Significance of time-course changes of serum bone markers after parathyroidectomy in patients with uraemic hyperparathyroidism. Nephrol Dial Transplant 22:1645–1657
31. Yajima A, Inaba M, Tominaga Y, Ito A (2008) Bone formation by minimodeling is more active than remodeling after parathyroidectomy. Kidney Int 74:775–781
32. Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D (2005) Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. J Clin Endocrinol Metab 90:135–141