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# The whole-PTH/intact-PTH ratio is a useful predictor of severity of secondary hyperparathyroidism

Motoko Tanaka[1], Hirotaka Komaba[2], Kazuko Itoh[1], Kazunori Matsushita[1], Kazutaka Matshushita[1], Yasuhiro Hamada[2], Hideki Fujii[2] and Masafumi Fukagawa[2]

[1]Department of Nephrology, Akebono Clinic, Kumamoto and [2]Division of Nephrology and Kidney Center, Kobe University School of Medicine, Kobe, Japan

## Abstract

**Background.** The newer parathyroid hormone (PTH) assay, whole-PTH, uses an antibody that binds the region harbouring the first amino acid, making it specific for the complete molecule, 1–84-PTH. Especially among dialysis patients, it has been reported that the level of whole-PTH can be calculated as ∼60% of their intact-PTH value. In addition, since 1–84-PTH is part of intact-PTH, the whole-PTH/intact-PTH ratio should not theoretically exceed 1. However, an abnormally high 1–84-PTH/intact-PTH ratio is reported in a few patients with parathyroid carcinoma, primary hyperparathyroidism and secondary hyperparathyroidism. In this study, we examined the correlation between the 1–84-PTH/intact-PTH ratio and the severity of hyperparathyroidism in patients on haemodialysis (HD).

**Patients and methods.** The study population comprised 196 HD patients (males 113, females 83, age 67.4 ± 13.6 years, HD period 8.1 ± 7.3 years; mean ± SD). The whole-PTH/intact-PTH ratio was compared in patients with high PTH levels (intact-PTH ≥300 pg/ml; high PTH group, $n = 32$), moderate PTH levels (intact-PTH >150–<300 pg/ml; moderate PTH group, $n = 50$) and low PTH levels (intact-PTH <150 pg/ml; low PTH group, $n = 114$). The ratio was also compared in 25 patients with at least one enlarged gland >0.5 $cm^3$ suggesting nodular hyperplasia, as determined by power Doppler ultrasonography (hyperplasia group) with seven patients without enlarged gland (non-hyperplasia group) and six patients who had undergone total parathyroidectomy (post-PTx group).

**Results.** The whole-PTH/intact-PTH ratio of the high PTH group (0.68 ± 0.1) was significantly higher than those of the moderate (0.61 ± 0.1, $P < 0.001$) and low (0.52 ± 0.1, $P < 0.001$) groups. Moreover, the ratio was significantly higher in the hyperplasia group (0.70 ± 0.1) than those in the non-hyperplasia group (0.59 ± 0.1, $P < 0.05$) and post-PTx group (0.456 ± 0.12, $P < 0.001$).

**Conclusions.** The whole-PTH/intact-PTH ratio correlated with the severity of hyperparathyroidism. Our results suggest that the ratio might be a useful predictor of severity of secondary hyperparathyroidism in HD patients.

**Keywords:** 1–84-PTH; haemodialysis; new molecular form of PTH; secondary hyperparathyroidism; whole-PTH/intact-PTH ratio

## Background

Secondary hyperparathyroidism with marked parathyroid hyperplasia is one of the most important complications in patients on chronic dialysis [1,2]. Large parathyroid glands represent nodular hyperplasia containing monoclonal proliferating cells [3–6] with low density of calcitriol receptors [7] and Ca-sensing receptors [8,9], and are therefore resistant to medical therapy, including calcitriol. When one or more parathyroid glands progress to the stage of nodular hyperplasia, it is usually difficult to control parathyroid hormone (PTH) secretion even by vitamin D3-based therapies [10,11].

As the second-generation assay, the intact-PTH assay recognizes 1–84-PTH as well as amino terminally truncated PTH fragments, i.e. large carboxy-terminal PTH fragments (C-PTH fragments). On the other hand, as the third generation assay which specifically recognizes bioactive 1–84-PTH, the whole-PTH assay was developed in 2003 and is now available in clinical practice [12,13].

It has been reported that the whole-PTH levels correlate with those of intact-PTH in healthy individuals, patients with primary hyperparathyroidism [14], HD patients [15] and patients with secondary hyperparathyroidism [16]. Especially among dialysis patients, it has been reported that the level of whole-PTH can be calculated as ∼60% of their intact-PTH value [15,16]. In addition, since 1–84-PTH is part of intact-PTH, the whole-PTH/intact-PTH ratio should not theoretically exceed 1.

However, it has been reported recently that an abnormally high whole-PTH/intact-PTH ratio could be detected in some patients with parathyroid carcinoma or primary hyperparathyroidism. Moreover, the presence of a new molecular form of PTH that cannot be detected by the

*Correspondence and offprint requests to*: Motoko Tanaka, Department of Nephrology, Akebono Clinic, 5-1-1 Shirafuji-machi, Kumamoto 861-4112, Japan. Tel: +81-96-358-7211; Fax: +81-96-358-7226; E-mail: tanaka@matusita-kai.or.jp

intact-PTH assay but by whole-PTH assay was confirmed in such patients [17,18]. In addition, we have recently reported two cases of secondary hyperparathyroidism with an abnormally high whole-PTH/intact-PTH ratio, suggesting the presence of a molecular form of PTH in patients with chronic kidney disease [19–21]. However, the clinical significance of this molecular form of PTH has not been clarified in patients with chronic kidney disease.

The present study investigated whether the use of the plasma whole-PTH/intact-PTH ratio enhances the noninvasive prediction of the severity of secondary hyperparathyroidism in patients on dialysis.

## Subjects and methods

The study population was 196 HD patients (males 113, females 83; age 67.4 ± 13.6 years, HD period 8.1 ± 7.3 years, mean ± SD) in our clinic. We measured serum intact-PTH levels (Elecsys PTH; Roche Diagnostics, Mannheim, Germany; normal range, 15–65 pg/mL) and whole-PTH levels [whole PTH$^{TM}$(1–84) Specific IRMA Assay; Scantibodies Laboratory, Inc., Santee, CA, USA; normal range, 9–39 pg/ml] for all these patients. We examined the correlation between the whole-PTH/intact-PTH ratio and the severity of secondary hyperparathyroidism in patients on dialysis. We used two markers for the severity of secondary hyperparathyroidism; one was the intact-PTH concentration and the other was the parathyroid gland volume determined by power Doppler ultrasonography, because previous studies [10] showed that the size of the enlarged gland is considered to be the best indicator of the presence of nodular hyperplasia and >90% of parathyroid glands >1 cm in diameter or 0.5 cm$^3$ in volume have been shown to contain nodular hyperplasia.

First, we compared the whole-PTH /intact-PTH ratio of 32 patients with high PTH levels (intact-PTH ≥300 pg /ml; high PTH group) with those of patients with moderate PTH levels (intact-PTH >150 to <300 pg/ml; moderate PTH group, $n = 50$) and low PTH levels (intact-PTH <150 pg/ml; low PTH group, $n = 114$). Next, 32 patients in the high PTH group were divided into two groups: 25 patients with at least one enlarged gland >0.5 cm$^3$, as determined by power Doppler ultrasonography (hyperplasia group), and 7 patients without enlarged gland (non-hyperplasia group). Then, we compared the whole-PTH/intact-PTH ratio of 25 patients in the hyperplasia group with 7 patients of the non-hyperplasia group and 6 patients who had undergone total parathyroidectomy with autotransplantation (post-PTx group). Written informed consent for this study was obtained from all patients following a detailed explanation.

## Results

### *Whole-PTH/intact-PTH ratio according to PTH levels in HD patients*

Average of the whole-PTH/intact-PTH ratio of all patients was 0.57 ± 0.14. Figure 1 shows the correlation between the whole-PTH/intact-PTH ratio and intact-PTH level in the high, moderate and low PTH groups. The ratio was significantly higher in the high PTH group (0.68 ± 0.1) than those in the moderate PTH group (0.61 ± 0.1, $P < 0.01$) and low PTH group (0.52 ± 0.1, $P < 0.001$). A significantly high correlation between whole-PTH and intact-PTH was observed in the patient population as a whole ($r = 0.975$, $y = -12.0 + 0.699x$), as well as in each group; however, the slope of each group showed a trend to increase in association with the severity of hyperparathyroidism (low group, 0.637; moderate group, 0.673; high group, 0.737).

### *Effect of nodular hyperplasia on the whole-PTH/intact-PTH ratio*

Figure 2 shows the correlation between the whole-PTH/intact-PTH ratio and intact-PTH levels in the hyperplasia-positive group, non-hyperplasia group and post-PTx group. The whole-PTH/intact-PTH ratio was significantly higher in the hyperplasia group (0.70 ± 0.1) than those of the non-hyperplasia group (0.59 ± 0.1, $P < 0.05$)

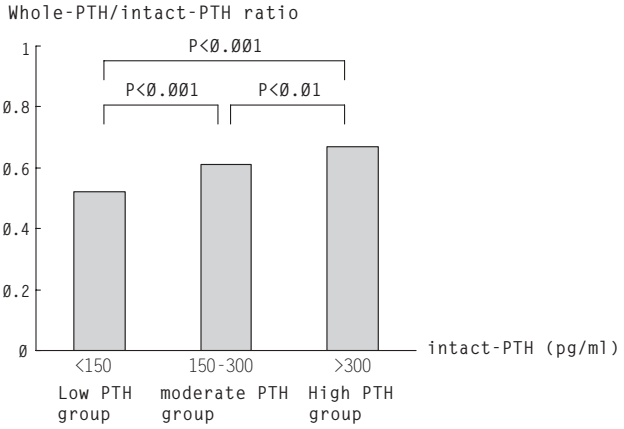


**Fig. 1.** Whole-PTH/intact-PTH ratio according to PTH levels in HD patients. Correlation between the whole-PTH/intact-PTH ratio and intact-PTH levels in the high PTH group, moderate PTH group and low PTH group. Data are mean ± SD.

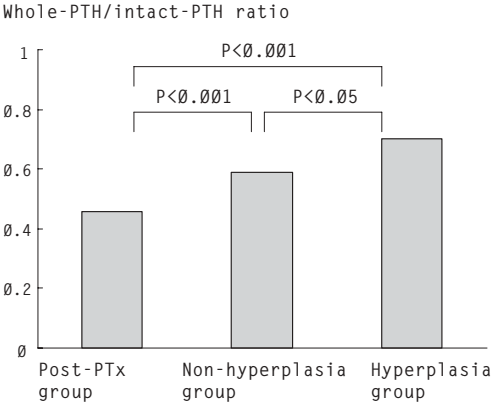


**Fig. 2.** Effect of nodular hyperplasia on the whole-PTH/intact-PTH ratio. Correlation between the whole-PTH/intact-PTH ratio and intact-PTH levels according to the size of parathyroid gland (presence or absence of hyperplasia). Data are mean ± SD.

and the post-PTx group ($0.456 \pm 0.12$, $P < 0.001$). With regard to the correlation between whole-PTH and intact-PTH levels, the slope of each group showed a trend to increase in association with the progression of hyperplasia (post-PTx group, 0.537; non-hyperplasia group, 0.590; hyperplasia group, 0.751).

## Discussion

The present study demonstrated a positive correlation between whole-PTH and intact-PTH in all groups, but the whole-PTH/intact-PTH ratio was significantly higher in patients with a high PTH level (intact-PTH $\geq$300 pg/ml). Moreover, a significantly high whole-PTH/intact-PTH ratio was observed in patients with nodular hyperplasia. These results suggest that a higher stage of parathyroid hyperplasia is associated with the increased whole-PTH/intact-PTH ratio.

Monier–Faugere *et al*. [22] proposed that the use of the plasma 1–84-PTH/C-PTH fragment ratio could enhance the noninvasive assessment of bone turnover in patients on dialysis. However, this is controversial at present because bone biopsy is too difficult to perform for routine examination for all patients. Here we propose the use of the whole-PTH/intact-PTH ratio for evaluation of the severity of secondary hyperparathyroidism.

Recent studies reported the presence of an abnormally high whole-PTH/intact-PTH ratio in a few patients with parathyroid carcinoma, primary hyperparathyroidism and secondary hyperparathyroidism, and demonstrated the presence of a new molecular form PTH as the cause [17–21]. In the previous studies, we confirmed that the parathyroid gland with nodular hyperplasia produced the new molecular form of PTH [19,20]. Moreover, HPLC analysis revealed that this new molecular form of PTH cannot be recognized by the intact-PTH assay but only by the 1–84-PTH assay because it has a modified 15–20 region of the N-terminal amino acids. These results mean that patients with high levels of the new molecular form of PTH must have a higher whole-PTH/intact-PTH ratio.

D'Amour *et al*. reported that the presence of the new molecular form of PTH was confirmed in 8% of healthy individuals, 25% of patients with primary hyperparathyroidism and 22% of patients with secondary hyperparathyroidism [18]. Thus, the highest proportions of patients who have this new molecular form of PTH are those with primary hyperparathyroidism [18], followed by patients with secondary hyperparathyroidism. Moreover, Yamashita *et al*. [14] reported that the whole-PTH/intact-PTH ratio of patients with primary hyperparathyroidism was higher than that of secondary hyperparathyroidism. These results might be due to the higher presence of the new molecular form of PTH in patients with primary hyperparathyroidism than in patients with secondary hyperparathyroidism [18]. Higher level of the new molecular form of PTH may involve in the higher whole-PTH/intact-PTH ratio and the new molecular form of PTH may be an independent bioactive factor for secondary hyperparathyroidism.

Kazama *et al*. [23] reported that intravenous maxacalcitol therapy, a vitamin D analogue, for patients with secondary hyperparathyroidism results in greater falls in serum whole-PTH levels compared with intact-PTH levels. Their results indicate possible differences in response to vitamin D therapy between whole-PTH and intact PTH. Moreover, we demonstrated that the whole-PTH/intact-PTH ratio in patients who had undergone parathyroidectomy was the lowest of any stage of hyperparathyroidism in HD patients. Thus, decreased severity of secondary hyperparathyroidism by intravenous maxacalcitol therapy and parathyroidectomy led to a decreased whole-PTH/intact-PTH ratio. These results should be confirmed in future studies of a larger population of HD patients.

In summary, the whole-PTH/intact-PTH ratio correlates with the severity of hyperparathyroidism in HD patients. Our results suggest that the whole-PTH/intact-PTH ratio might be a useful predictor of the severity of secondary hyperparathyroidism in HD patients.

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*Conflict of interest statement.* None declared.

## References

1. Malluche HH, Faugere MC. Renal bone disease 1990: an unmet challenge for the nephrologist. *Kidney Int* 1990; 38: 193–211
2. Parfitt AM. Parathyroid growth: normal and abnormal. In: Bilezikian JP, Marcus R, Levine MA (eds). *The Parathyroid: Basic & Clinical Concepts*. New York: Raven Press, 1994, 373
3. Tominaga Y, Grimelius L, Falkmer UG *et al*. DNA ploidy pattern of parathyroid parenchymal cells in renal secondary hyperparathyroidism with relapse. *Anal Cell Pathol* 1991; 3: 325–333
4. Tominaga Y, Tanaka Y, Sato K *et al*. Recurrent renal hyperparathyroidism and DNA analysis of autografted parathyroid tissue. *World Surg* 1992; 16: 595–603
5. Tominaga Y, Tanaka Y, Sato K *et al*. Histopathology, pathophysiology, and indications for surgical treatment of renal hyperparathyroidism. *Semin Surg Oncol* 1997; 13: 78–86
6. Arnold A, Brown MF, Urena P *et al*. Monoclonality of parathyroid tumors in chronic renal failure and in primary parathyroid hyperplasia. *J Clin Invest* 1995; 95: 2047–2053
7. Fukuda N, Tanaka H, Tominaga Y *et al*. Decreased 1,25-dihydroxyvitamin D3 receptor density associated with a more severe form of parathyroid hyperplasia in chronic uremic patients. *J Clin Invest* 1993; 92: 1436–1443
8. Kifor O, Moore FD Jr, Wang P *et al*. Reduced immunostaining for the extracellular $Ca^{2+}$-sensing receptor in primary and uremic secondary hyperparathyroidism. *J Clin Endocrinol Metab* 1996; 81: 1598–1606
9. Gogusev J, Duchambon P, Hory B *et al*. Depressed expression of calcium receptor in parathyroid gland tissue of patients with hyperparathyroidism. *Kidney Int* 1997; 51: 328–336
10. Fukagawa M, Kitaoka M, Inazawa T *et al*. Imaging of the parathyroid in chronic renal failure: diagnostic and therapeutic aspects. *Curr Opin Nephrol Hypertens* 1997; 6: 349–355
11. Fukagawa M, Tominaga Y, Kitaoka M *et al*. Medical and surgical aspects of parathyroidectomy. *Kidney Int* 1999; 73: S65–S69
12. Blind E, Schmidt-Gayk H, Scharla S *et al*. Two-site assay of intact parathyroid hormone in the investigation of primary hyperparathyroidism and other disorders of calcium metabolism compared with a midregion assay. *J Clin Endocrinol Metab* 1988; 67: 353–360
13. Goodman WG. New assays for parathyroid hormone (PTH) and the relevance of PTH fragments in renal failure. *Kidney Int* 2003; 87: S120–S124

14. Yamashita H, Gao P, Cantor T *et al*. Comparison of parathyroid hormone levels from the intact and whole parathyroid hormone assays after parathyroidectomy for primary and secondary hyperparathyroidism. *Surgery* 2004; 135: 149–156
15. Nakanishi S, Kazama JJ, Shigematsu T *et al*. Comparison of intact PTH assay and whole PTH assay in long-term dialysis patients. *Am J Kidney Dis* 2001; 38(Suppl 1): S172–S174
16. Inaba M, Nakatsuka K, Imanishi Y *et al*. Technical and clinical characterization of the Bio-PTH (1–84) immunochemiluminometric assay and comparison with a second-generation assay for parathyroid hormone. *Clin Chem* 2004; 50: 385–390
17. Rubin MR, D'Amour P, Brossard JH *et al*. A molecular form of PTH distinct from PTH (1–84) is produced in parathyroid carcinoma. *J Bone Mineral Res* 2004; 19(Suppl 1): S327
18. D'Amour P, Brossard JH, Rousseau L *et al*. Amino-terminal form of parathyroid hormone (PTH) with immunologic similarities to hPTH(1–84) is overproduced in primary and secondary hyperparathyroidism. *Clin Chem* 2003; 49: 2037–2044
19. Tanaka M, Itoh K, Matsushita K *et al*. Normalization of reversed bio-intact-PTH(1–84)/intact-PTH ratio after parathyroidectomy in a patient with severe secondary hyperparathyroidism. *Clin Nephrol* 2005; 64: 69–72
20. Arakawa T, D'Amour P, Rousseau L *et al*. Overproduction and secretion of a novel amino-terminal form of PTH from a severe type of parathyroid hyperplasia in uremia. *Clin J Am Soc Nephrol* 2006; 1: 525–531
21. Fukagawa M, Hamada Y, Nakanishi S *et al*. The kidney and bone metabolism: nephrologists' point of view. *J Bone Miner Metab* 2006; 24: 434–438
22. Monier-Faugere MC, Geng Z, Mawad H *et al*. Improved assessment of bone turnover by the PTH-(1–84)/large C-PTH fragments ratio in ESRD patients. *Kidney Int* 2001; 60: 1460–1468
23. Kazama JJ, Omori K, Higuchi N *et al*. Intact PTH assay overestimates true 1–84 PTH levels after maxacalcitol therapy in dialysis patients with secondary hyperparathyroidism. *Nephrol Dial Transplant* 2004; 19: 892–897

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