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Comparison between Whole and Intact Parathyroid Hormone Assays

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Abstract: The standard measurement of parathyroid hormone (PTH) is the intact PTH (iPTH) assay, which is used for approximately 90% of Japanese dialysis patients. The iPTH assay reacts not only with 1–84 PTH, but also with large truncated fragments of non-1–84 PTH, including 7–84 PTH. On the other hand, the whole PTH assay is specific for 1–84 PTH. The aim of the current study was to define the validity of both whole and intact PTH assays. A total of 738 hemodialysis patients were enrolled from twelve dialysis services. The serum PTH level was evaluated by both intact and whole PTH assays simultaneously. Non-1–84 PTH was determined by subtracting the whole PTH value from that of the intact PTH assay. The median level of whole PTH was 121 pg/mL, and that of iPTH was 210 pg/mL. The whole PTH assay had a very high correlation with the iPTH assay ($r = 0.870$, $P < 0.001$). For 43 out of 738 patients (5.8%) the value for intact PTH—whole PTH was <0. Both assays significantly correlated with non-1–84 PTH ($P < 0.001$), while the iPTH assay, particularly, had a very high correlation with non-1–84 PTH ($r = 0.791$). As a whole, 18% of the total population was misclassified into a different Japanese guideline category. Stratified by Japanese guideline classifications, 28% of patients within an iPTH target range were misclassified. Using Bland–Altman plot analysis, as the serum PTH level increased, there was a large difference between two assays. Both PTH assays correlate strongly, although the whole PTH assay may be more useful for precise evaluation of PTH function than the iPTH assay. **Key Words:** Intact parathyroid hormone, non-1–84 parathyroid hormone, N-parathyroid hormone, whole parathyroid hormone.

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Secondary hyperparathyroidism is commonly observed in dialysis patients. Measurement of parathyroid hormone (PTH) values is used to assess the severity of hyperparathyroidism, to decide when to start a vitamin D receptor activator or cinacalcet, and

to monitor the effectiveness of treatment. The standard measurement of PTH is the intact PTH (iPTH) assay, which was developed in late 1980s. In Japan, the iPTH assay was used in approximately 90% of all dialysis patients in the data of Japanese Renal Data Registry 2009, although, the iPTH assay was shown to react not only with 1–84 PTH but also with large truncated fragments of non-1–84 PTH, including 7–84 PTH (1–4). In humans, 20–60% of PTH measured with the iPTH assay corresponds to non-1–84 PTH (1,3–5). In dialysis patients, the percentage of non-1–84 PTH calculated by the iPTH assay is generally greater than normal people (1–6). The whole PTH assay has been shown to be specific for 1–84 PTH. Serum concentrations of large, truncated fragments of non-1–84 PTH can be determined by subtracting the whole PTH value from that measured with the iPTH assay (7,8). In parathyroidectomized rats, a 7–84 PTH infusion, which is a main fragment of non-1–84 PTH, was shown to inhibit a calcemic action of simultaneously infused 1–84 PTH (7). These results suggest that large, truncated PTH fragments similar to 7–84 PTH may be an important cause of skeletal resistance to 1–84 PTH in uremia. In a study of hemodialysis patients, the 1–84 PTH/non-1–84 PTH ratio was less than 1 only in those patients with low bone turnover (8). This result also suggests that large carboxy-terminal fragments may antagonize the skeletal effects of 1–84 PTH. Moreover, the 7–84 PTH fragment, like other carboxy-terminal fragments, binds only to the carboxyl PTH receptor and does not affect the binding of 1–84 PTH to the PTH related peptide (PTHrP) receptor (9–11). Thus, it would appear that the 7–84 PTH fragment may decrease the calcemic action of 1–84 PTH through its interaction with the carboxyl PTH receptor. In order to assess the severity of hyperparathyroidism accurately, it is important to understand the characteristics and the differences of both whole and intact PTH assays.

The aim of the current study was to define the validity of both whole and intact PTH assays by assessing: (i) the comparison of distribution; (ii) the correlation between both assays; (iii) the association of both assays with patient characteristics; and (iv) the comparison between whole PTH and calculated 1–84 PTH levels.

PATIENTS AND METHODS

Patient selection

A total of 738 hemodialysis patients were enrolled in Japan from twelve hemodialysis clinics in five prefectures between June 2000 and May 2006. These associated clinics included: Tokai University School of Medicine, Sekisinkai Kawasaki Clinic, Dai2-Rokushima Clinic, Sekishin Clinic, Japan Red Cross Musashino Hospital, Nakano Clinic, Kyonan Clinic, Suda Clinic, Tokyo Women's Medical University, Mihama Narita Clinic, Matsushita-Kai Akebono Clinic, and Sumiyoshi Clinic Hospital. Entry criteria included having been hemodialysis patients in the preceding three months, the ability to provide informed consent for participation, and being of an age greater than 19 years.

Data collection and PTH assays

Blood used for PTH analyses was collected from the study participants as part of a special lab specimen draw. The serum PTH level was evaluated by both intact and whole PTH assays simultaneously. An EDTA-containing tube was collected before hemodialysis, kept on ice for 1 h, and immediately centrifuged at 1000 *g* for 10 min, separated and refrigerated. PTH has been shown to be stable for 72 h in refrigerated EDTA plasma (12). Specimens were stored at –20°C until they were thawed for analysis at DS Pharma Biomedical (Osaka, Japan).

A single incubation step immunoradiometric assay specific for whole PTH (1–84) was developed and optimized with the previously-mentioned assay reagents. Briefly, 200 μL of assay standards, controls, and patient samples were pipetted into appropriately labeled 12 mm × 7.5 mm polypropylene test-tubes. One hundred microliters of ^{125}I-labeled PTH-specific antibody tracer solution and one goat anti-PTH (39–84) polyclonal antibody-coated bead were added to all test-tubes (1–4). The immunochemical reaction was conducted at room temperature with shaking at 170 rpm for 18–22 h. During this assay incubation period, the immunochemical reaction forming the sandwich of (solid-phase goat anti-PTH (39–84) antibody)—(whole PTH (1–84))—(^{125}I-goat anti-PTH antibody) takes place in correlation with the amount or concentration of whole PTH (1–84) in the test sample. All beads in the test tubes, except the total count tube, were washed with the wash solution, and the radioactive signals from each bead were counted for 1 min using a gamma scintillation counter. The data were processed and calculated using nonlinear regression data reduction software.

Other laboratory measures

Other laboratory measures included measures of serum calcium, phosphate, albumin, alkaline phosphatase, total cholesterol, and HDL-cholesterol from dates that were closest available to the special lab draw date. Serum calcium was adjusted for albumin

using the formula: adjusted calcium = measured calcium – ((4.0 – serum albumin in g/dL)) (13). All calcium values reported and used in this analysis were corrected using the above formula. PTH values were log-transformed in some analyses due to their non-normal distributions.

Statistical analysis

Data are expressed as the mean ± SD. All statistical analyses were conducted using the DOCTOR SPSS II 18.0 program (SPSS Japan, Tokyo, Japan). Differences between groups were calculated using the Mann–Whitney *U*-test, the χ^2-test or ANOVA, where appropriate. Correlation coefficients were calculated by the Pearson method. The comparison of ranks between the whole and intact PTH values was performed using Student's *t*-test. A P value <0.05 was considered significant.

RESULTS

Baseline characteristics and laboratory data

As shown in Table 1, we studied 738 patients (58% male gender) with end-stage renal failure from five dialysis units. All patients underwent chronic hemodialysis treatment three times weekly. The median age of the patients was 60.0 years (range 9–103, mean 58.8 ± 12.6 years). The median vintage of hemodialysis was 132 months (range 2–1238, mean 145 ± 102 months). The underlying renal diseases were: chronic glomerulonephritis, 66%; diabetic nephropathy, 17%; hypertensive nephrosclerosis, 4%; and others, 13%. Of the patients, 24% had a history of cardiovascular disease. The ratio of use of vitamin D receptor activators (i.v. and oral) was 65%. The use of 3.0 mEq/L containing dialysate was 79% of the patients.

At entry, serum corrected calcium and phosphate values were 9.6 ± 0.9 mg/dL and 5.7 ± 1.4 mg/dL, respectively. Serum albumin and alkaline phosphatase concentrations were 3.8 ± 0.4 g/dL and 258 ± 118 IU/L, respectively. At baseline, serum total cholesterol and HDL-cholesterol values were 158 ± 35 mg/dL and 50 ± 16 mg/dL, respectively. The body mass index and Kt/V were 21.1 ± 3.2 kg/m^2 and 1.48 ± 0.28, respectively.

Distribution of serum whole and intact PTH levels

The median serum whole PTH level was 121 pg/mL (range 2–888, mean 164 ± 143 pg/mL; Table 1). The interquartile range of whole PTH was 63–223 pg/mL. The median iPTH was 210 pg/mL (range 3–1436, mean 259 ± 216 pg/mL), and the interquartile range was 111–346 pg/mL. The distribution of whole and iPTH was revealed in Figure 1. Both whole PTH and iPTH assays showed log-normal distribution. There were 224/738 (30.4%) patients with a whole PTH level between 35–105 pg/mL, which is the target range of the Japanese guidelines. Those with an iPTH level between 60–180 pg/mL numbered 221 of 738 (29.9%). Those with whole PTH level <35 pg/mL were 98/738 (13.3%), and those with an iPTH level <60 pg/mL numbered 106/678 (14.4%).

TABLE 1. *Patient baseline characteristics*

Characteristics	
N	738
Age (years)	59 ± 13
Gender (% male)	58
Duration of hemodialysis (months)	145 ± 102
Etiology of renal failure (%)	
Glomerulonephritis	66
Diabetes mellitus	17
Hypertension	4
Other	13
Comorbid conditions (%)	
Diabetes mellitus	18
Cardiovascular disease	24
Fracture	6
History of parathyroidectomy or PEIT	24
Treatment (%)	
Use of an anti-hypertension drug	74
Use of oral or injectable VDRA	65
Use of 3.0 mEq/L Ca-containing dialysate	79
Baseline laboratory tests	
Albumin (g/dL)	3.8 ± 0.4
Calcium (mg/dL)	9.4 ± 0.9
Corrected calcium (mg/dL)	9.6 ± 0.9
Phosphate (mg/dL)	5.7 ± 1.4
Alkaline phosphatase (U/L)	258 ± 118
Whole PTH (pg/mL)	164 ± 143
Median	121
Range	2–888
Intact PTH (pg/mL)	259 ± 216
Median	210
Interquartile range	3–1436
Total cholesterol (mg/dL)	158 ± 35
HDL cholesterol (mg/dL)	50 ± 16
Body mass index (kg/m^2)	21.1 ± 3.2
Kt/V	1.48 ± 0.28
nPCR (g/kg/day)	1.26 ± 0.49

HDL high-density lipoprotein; nPCR, normalized protein catabolic rate; PEIT, percutaneous parathyroid gland ethanol injection therapy; PTH, parathyroid hormone; VDRA, vitamin D receptor activator.

Correlation between serum whole PTH and iPTH levels

The association between whole and intact PTH is shown in Figure 2. The whole PTH assay had a very high correlation with iPTH, as shown below:

$$\text{Intact PTH} = \text{Whole PTH} \times 1.59$$
$$\text{Whole PTH} = \text{Intact PTH} \times 0.63$$
$$(r = 0.870,\ P < 0.001)$$

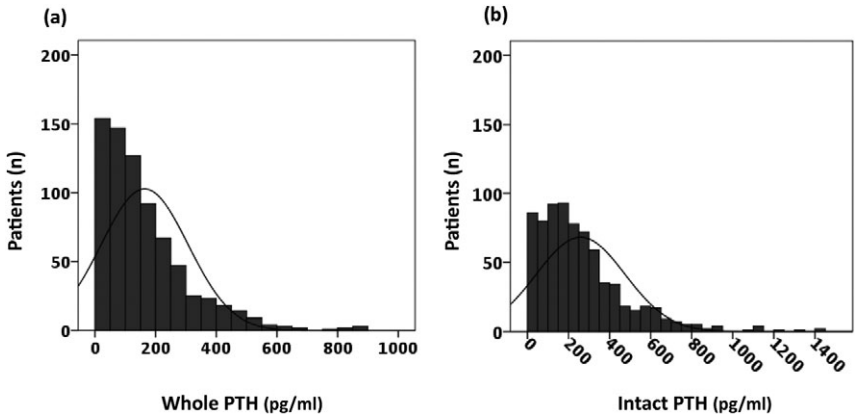

FIG. 1. Distribution of serum (a) whole parathyroid hormone (PTH), and (b) intact PTH levels. The median serum whole PTH level was 121 pg/mL (range 2–888, mean 164 ± 143 pg/mL). The median intact PTH was 210 pg/mL (range 3–1436, mean 259 ± 216 pg/mL). Both assays showed log-normal distribution.

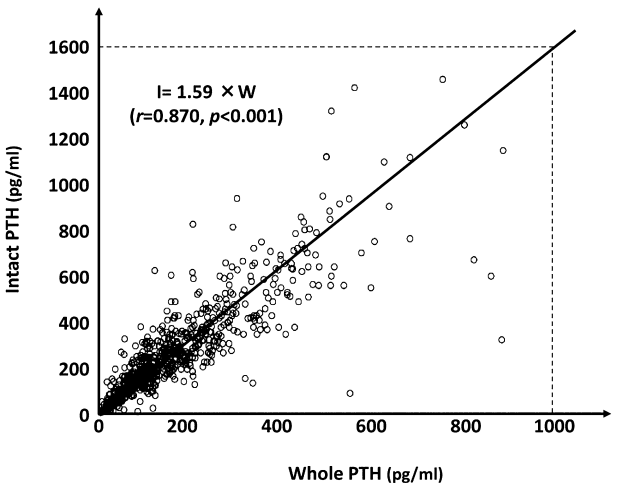

FIG. 2. Correlation between serum whole parathyroid hormone (PTH) and intact PTH levels. The whole PTH assay had a very high correlation with the intact PTH assay ($r = 0.870$, $P < 0.001$).

Then, we divided patients into three categories according to serum iPTH level: ≤60 pg/mL, 61–180 pg/mL, and >180 pg/mL (Fig. 3). In each category, the correlation coefficients were different. The correlation coefficient with iPTH below 60 pg/mL was 1.29, which was obviously lower than 1.59. As the serum PTH level increased, the correlation coefficient between whole and intact PTH levels increased.

Non-1–84 PTH

Serum concentrations of large, truncated fragments of non-1–84 PTH can be determined by subtracting the whole PTH value from that measured with the iPTH assay (7,8). Theoretically, the serum PTH level measured with the iPTH assay is higher than that with the whole PTH assay; however, rare exceptions to this rule have been reported in some

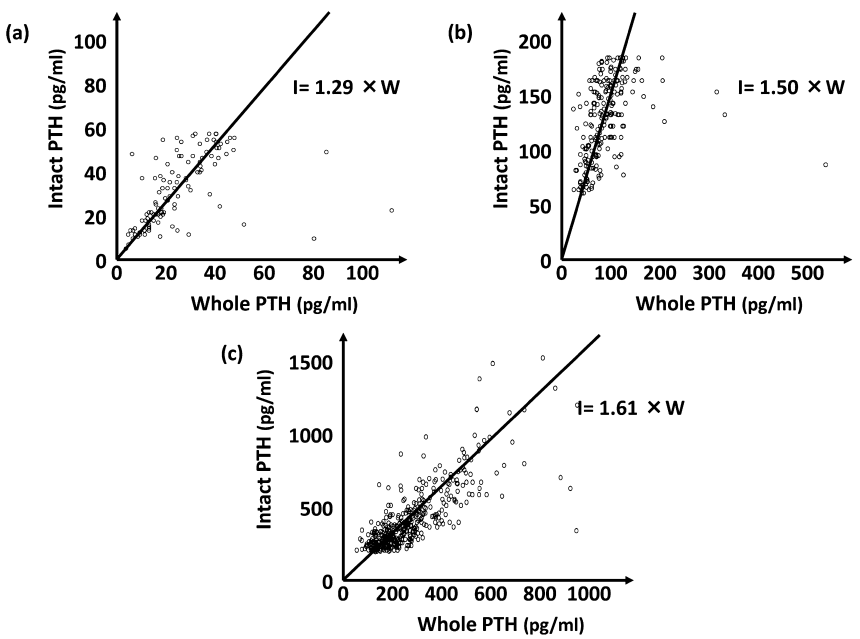

FIG. 3. Correlation between both assays in each intact parathyroid hormone (PTH) level: (a) ≤60 pg/mL; (b) 61–180 pg/mL; and (c) >180 pg/mL. In patients with low PTH levels (<60 pg/mL), the correlation coefficient was comparably low.

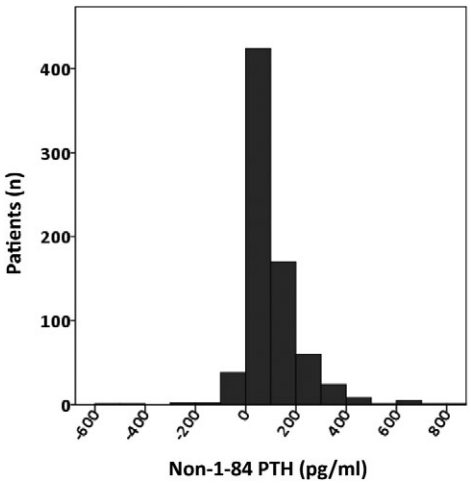

FIG. 4. Distribution of serum non-1–84 parathyroid hormone (PTH) level. There were 43/738 patients (5.8%) with (intact PTH – whole PTH) < 0.

patients, associated with N-PTH overproduction (14–16). As shown in Figure 4, the patients with (iPTH—whole PTH) < 0 numbered 43/738 (5.8%). The association between non-1–84 PTH and each assay is shown in Figure 5. Both assays were significantly correlated with non-1–84 PTH ($P < 0.001$). In particular, the iPTH assay had a very high correlation with non-1–84 PTH ($r = 0.791$).

Association of whole PTH, iPTH, and non-1–84 PTH with patient characteristics

The patients who were younger than 65 years and did not have diabetes mellitus, high calcium, high phosphate, or high alkaline phosphatase had higher whole and intact PTH levels, significantly (Table 2). Among these, serum calcium, phosphate, and alkaline phosphatase levels were significantly related with non-1–84 PTH.

In multivariate linear regression analysis, patient characteristics associated with greater whole PTH levels included male gender, dialysate calcium 3.0 mEq/L versus 2.5 mEq/L, higher corrected calcium, higher phosphate, and higher alkaline phosphatase levels (Table 3). These results were all the same as the iPTH assay. Patient characteristics associated with higher non-1–84 PTH levels included dialysate calcium 3.0 mEq/L, higher serum albumin, higher calcium, higher phosphate, and higher alkaline phosphatase levels.

Comparison between whole PTH and calculated 1–84 PTH levels

When the 1–84 fraction was calculated using 63% of the iPTH, 18% (131/738) of the total population was misclassified into a different Japanese guideline category. The percentage agreement was 82%. Stratified by Japanese guideline classifications, 24% (27/114) of those below target range were misclassified, while 28% (60/214) and 11% (44/410) of those within or above target range, respectively, were misclassified. The Bland–Altman plot, showing the difference between whole PTH and calculated 1–84 PTH plotted against the mean of the two values, reveals that at low PTH levels, there are a few significant differences between the two assays, but that, as the PTH levels increase, there is a large difference between the two measures (Fig. 6).

DISCUSSION

The first objective of the present study was to elucidate a difference between whole and intact PTH assays. At first, we investigated the distribution of both assays and, as shown in Figure 1, both assays revealed a log-normal distribution. Patients whose PTH level was within the Japanese target range were about 30% in both assays. In accordance with some previous reports (17–20), there was a strong correlation ($r = 0.870$) between both assays in the present

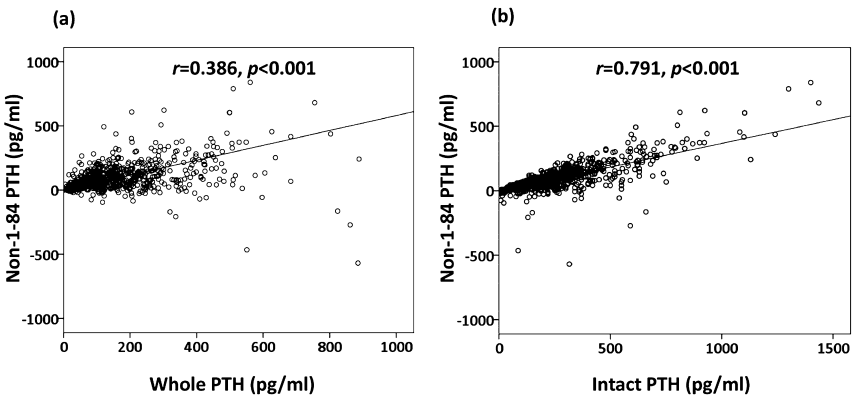

FIG. 5. Correlation between non-1–84 parathyroid hormone (PTH) and (a) the whole PTH and (b) intact PTH assays. Both assays were significantly correlated with non-1–84 PTH ($P < 0.001$). In particular, the intact PTH assay had a very high correlation with non-1–84 PTH ($r = 0.791$).

TABLE 2. *Whole parathyroid hormone (PTH), intact PTH and non-1–84 PTH by patient characteristics*

Characteristics	Whole PTH (pg/mL)		Intact PTH (pg/mL)		Non-1–84 PTH (pg/mL)	
	Median (IQR)	*P* value	Median (IQR)	*P* value	Median (IQR)	*P* value
Age						
<65 years (*N* = 498)	134 (70–238)	<0.01	224 (120–360)	<0.01	75 (27–147)	0.06
≥65 years (*N* = 240)	105 (43–204)		181 (85–280)		64 (23–110)	
Gender						
Male (*N* = 431)	130 (63–233)	0.18	219 (110–360)	0.32	68 (24–134)	0.85
Female (*N* = 307)	109 (60–212)		201 (102–336)		75 (27–137)	
Hemodialysis vintage						
<132 months (*N* = 369)	115 (54–209)	0.05	196 (101–318)	0.22	71 (31–133)	0.91
≥132 months (*N* = 369)	127 (70–239)		220 (119–355)		70 (19–142)	
Diabetes						
Absent (*N* = 603)	127 (66–237)	<0.01	221 (117–353)	<0.01	75 (24–144)	0.07
Present (*N* = 135)	101 (52–172)		160 (93–266)		58 (28–101)	
Corrected calcium						
<9.4 mg/dL (*N* = 359)	110 (59–204)	<0.01	180 (105–302)	<0.01	58 (25–108)	<0.01
≥9.4 mg/dL (*N* = 379)	133 (64–237)		242 (110–370)		86 (25–162)	
Phosphate						
<5.6 mg/dL (*N* = 351)	101 (49–177)	<0.01	180 (88–285)	<0.01	60 (22–115)	<0.01
≥5.6 mg/dL (*N* = 387)	150 (79–272)		244 (130–420)		77 (30–162)	
Alkaline phosphatase						
<234 U/L (*N* = 359)	104 (52–196)	<0.01	176 (91–290)	<0.01	58 (18–113)	<0.01
≥234 U/L (*N* = 353)	141 (76–245)		240 (140–386)		80 (34–162)	

IQR, interquartile range.

study. The correlation coefficient was 1.59, which was almost the same as that of the Japanese guidelines (21). When we divided patients into three categories according to the serum iPTH level, the correlation coefficient with iPTH below 60 pg/mL was 1.29, which was obviously lower than 1.59. This difference of the coefficient would be due to N-PTH overproduction or some PTH fractions, such as 7–84 PTH fragment. During hypercalcemia, the proportional decrease in carboxyl terminal fragments is less than that of 1–84 PTH (22–24). In hemodialysis patients, the percent of non-1–84 PTH was shown to directly correlate with the predialysis serum calcium concentration, with an increase in the serum calcium concentration associated with a reduction in the ratio of 1–84 PTH/non-1–84 PTH (7,8). These results suggest that hypercalcemia or calcium load would induce the fragmentation of 1–84 PTH and lead to the increase of the non-1–84 PTH value.

In the category with iPTH <60 pg/mL, iPTH is considered to be underestimated. Twenty-four percent of the low iPTH category showed serum whole PTH levels within the Japanese target range (35–105 pg/mL). In the category with iPTH 61–180 pg/mL, 22% of the patients showed high whole PTH levels (>105 pg/mL). On the other hand, in the high iPTH category, 11% of the patients revealed serum whole PTH levels within the Japanese target range (35–105 pg/mL). The distribution of both assays was alike and the correlation between both assays was high, although there were a considerable number of misclassifications.

We elucidated an association between each PTH assay and the patient characteristics. In multivariate

TABLE 3. *Adjusted differences in whole parathyroid hormone (PTH), intact PTH and non-1–84 PTH by patient characteristics*

Characteristics	Whole PTH (pg/mL)		Intact PTH (pg/mL)		Non-1–84 PTH (pg/mL)	
	β	P value	β	P value	β	P value
Age, per 10 years	–0.06	0.15	–0.03	0.51	0.21	0.58
Female vs. male	–0.07	0.04	–0.06	0.09	–0.21	0.57
Hemodialysis vintage, per 10 months	0.02	0.60	0.003	0.94	–0.17	0.66
Diabetes mellitus vs. no diabetes mellitus	–0.05	0.22	–0.04	0.29	–0.16	0.68
Dialysate calcium 3.0 mEq/L vs. 2.5 mEq/L	0.09	0.01	0.11	<0.01	0.87	0.02
Albumin, per g/dL	–0.05	0.21	0.05	0.20	0.18	<0.01
Corrected calcium, per mg/dL	0.12	<0.01	0.13	<0.01	0.09	0.03
Phosphate, per mg/dL	0.27	<0.01	0.28	<0.01	0.19	<0.01
Alkaline phosphatase, per U/L	0.19	<0.01	0.23	<0.01	0.20	<0.01

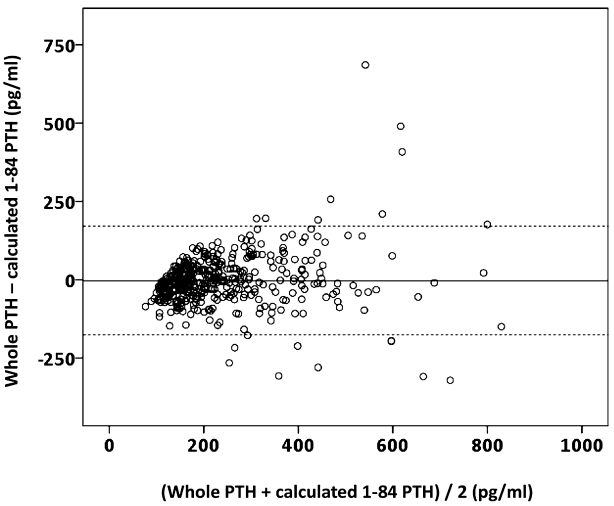

FIG. 6. Bland–Altman plot of whole parathyroid hormone (PTH) versus calculated 1–84 PTH. At low PTH levels, there are a few significant differences between two assays; however, as the PTH levels increase, there is a large difference between the two measures (calculated 1–84 PTH = intact PTH × 0.63).

analysis using a linear regression model, the patients with both greater whole and intact PTH levels include higher dialysate calcium concentrations and higher serum calcium levels. Hypercalcemia usually inhibits PTH secretion. Elevation of the serum calcium level with a high PTH state was considered due to medical therapy, such as with vitamin D or calcium carbonate. The serum non-1–84 PTH level significantly correlated with dialysate calcium 3.0 mEq/L, higher serum albumin, higher calcium, higher phosphate, and higher alkaline phosphate levels. These results indicated that a high serum calcium level or calcium overload would cause an increase of non-1–84 PTH production.

The amount of 1–84 PTH was calculated using 63% of the iPTH. As a whole, 18% of the total population was misclassified into a different Japanese guideline category. Stratified by Japanese guideline classifications, 28% of patients within the iPTH target range were misclassified. The Bland–Altman plot (Fig. 6), showing the difference between whole PTH and calculated 1–84 PTH (=iPTH × 0.63) plotted against the mean of the two values. There is not a systematic bias in this comparison. As the PTH levels increase, there is a large difference between the two measures. There were many outliers in the whole PTH side (the upper part of the graph). It is probably due to N-PTH overproduction. Some outliers in the calculated 1–84 PTH side (the lower part of the graph) would reveal PTH fragmentations.

There are several limitations in the present study. The first is that we did not have data for mortality, onset of cardiovascular disease, or fracture. If possible, we should elucidate an association between the serum PTH level and mortality or fracture in each PTH assay. Melamed et al. (25) had reported that an elevated 1–84 PTH value was significantly associated with an increased risk of death, whereas iPTH was not significantly associated with mortality. Lehmann et al. (26) took bone biopsies from 132 patients with chronic kidney disease in stages 3–5 and evaluated the association of bone histomorphometry with the iPTH and Bio-Intact PTH assays. Both assays effectively identified patients with reduced bone turnover. There was no difference between both assays. According to these reports, the difference of the PTH assays may not have much influence on the risk of either mortality or fracture.

In summary, in this cohort of dialysis patients, although the distribution of both assays was alike and the correlation between both assays was high, there were some misclassifications. Eighteen percent of the total population was misclassified into a different Japanese guideline category. As the PTH levels increased, there was a large difference between the two measures. In conclusion, both PTH assays were strongly correlated, although, the whole PTH assay may be more useful for precise evaluation of PTH activity than the iPTH assay.

Conflict of interests: The authors have no conflict of interests.

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