



Changes in the whole/intact parathyroid hormone ratio and their clinical implications in patients with chronic kidney disease

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Received: 18 October 2019 / Accepted: 21 December 2019 / Published online: 9 January 2020
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Abstract

Background Although a previous study has reported the relationship between intact parathyroid hormone (iPTH) and whole parathyroid hormone (wPTH) levels in patients undergoing dialysis, the w/i PTH ratio (whole/intact PTH ratio) among predialysis chronic kidney disease (CKD) patients remains unclear. The present study therefore aimed to examine the relationship between w/i PTH ratio and kidney function and determine other factors affecting the w/i PTH ratio.

Methods An observational study including 773 predialysis CKD patients was conducted. The correlation between w/i PTH ratio and kidney function, as well as clinical factors at different CKD stages, were assessed using univariate and multivariate analyses. In addition, the relationship between w/i PTH ratio and composite renal outcome [kidney transplantation, dialysis, and 30% decline in estimated glomerular filtration rate (eGFR)] was examined.

Results The w/i PTH ratio decreased as the CKD stage progressed. Patients in each CKD stage (1/2, 3, 4, and 5) had a w/i PTH ratio of 0.85, 0.81, 0.78, and 0.59, respectively. The inflection point in the correlation lines between eGFR and w/i PTH ratio was 24.1 mL/min/1.73 m². In multivariate analysis, the w/i PTH ratio was significantly correlated with serum calcium levels only in the CKD5 group and with eGFR in the CKD3, CKD4 and CKD5 group. Furthermore, w/i PTH ratio, eGFR, serum phosphate levels, and urinary protein/creatinine ratio were determined to be significant independent predictors for composite renal outcome.

Conclusions Our study demonstrated that changes in the w/i PTH ratio were associated with kidney function, abnormal mineral metabolism, and renal outcome.

Keywords Intact PTH · Whole PTH · whole/intact PTH ratio · Chronic kidney disease

Introduction

The kidney is responsible for maintaining serum calcium, serum phosphate, and bone metabolism balance via several pathways. From the early stages of chronic kidney disease (CKD), serum fibroblast growth factor 23 (FGF23) levels increase, active vitamin D levels decrease, and parathyroid hormone (PTH) secretion is stimulated to keep serum calcium and phosphate levels within normal range [1]. However, as CKD progresses from early to advanced stages, physiological mechanisms gradually break down, thereby resulting in hypocalcemia, hyperphosphatemia,

and hyperparathyroidism. Such mineral metabolism abnormalities have been closely associated with cardiovascular disease and mortality [2, 3]. Therefore, the Japanese Society of Dialysis Therapy (JSDT) and the 2017 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have recommended the control of serum intact PTH (iPTH) level within the appropriate ranges (JSDT, 60–240 pg/mL; KDIGO, 130–585 pg/mL) given that maintaining serum iPTH levels within such ranges has been associated with a lower risk for death in patients undergoing dialysis [4, 5].

Recent developments in the assay system for PTH measurement have led to the availability of a third-generation assay. Considering that the second-generation PTH assay (iPTH assay) measures 1–84 and 7–84 PTH fragments, such an assay would yield higher levels compared to a third-generation assay [whole PTH (wPTH) assay], which measures only 1–84 PTH fragment. However, only a few reports have suggested the superiority of a wPTH assay over an iPTH

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assay [6], while the current accumulation of evidence has revealed that an iPTH assay has been widely used in clinical settings.

wPTH is the biologically active form of PTH. On the other hand, 7–84 PTH is a degradation product in the parathyroid gland and liver and inhibits the wPTH activity and secretion [7, 8]. Although the detailed mechanisms and clinical implications of changes in the whole/intact (w/i) PTH ratio remain unclear, it seems to reflect not only the balance between wPTH production and degradation, but also the biological action of PTH.

In patients undergoing maintenance dialysis, the JSDT guideline recommended a target range for wPTH, which can be estimated by dividing the target iPTH range by 1.7. Considering this formula, the w/i PTH ratio could be determined as 0.58 in those patients [9].

However, only a few studies including a small number of patients have reported on the w/i PTH ratio at each CKD stage among those who did not undergo dialysis [10–13]. Therefore, the present study examines the relationship between w/i PTH ratio and kidney function, determines clinical factors related to the w/i PTH ratio, and discusses the clinical implication of the w/i PTH ratio.

Materials and methods

Study design and population

This was a retrospective observational study conducted in accordance with the principles stated in the Declaration of Helsinki. Our study protocol was approved by the appropriate institutional review committee of Kobe University Graduate School of Medicine (no. 1871). Informed consent was obtained from all participants.

This study included 954 predialysis patients at different CKD stages who visited our department between December 2014 and December 2015. All patients satisfied the KDIGO guideline criteria for CKD [14]. Patients who were diagnosed with primary hyperparathyroidism, underwent kidney transplantation, and developed acute myocardial infarction, acute heart failure, or serious infection were excluded from the present study. Those who had wPTH levels higher than their iPTH levels, had insufficient clinical data, and did not provide informed consent were also excluded. Among the 954 patients, 181 were excluded because of the aforementioned reasons (primary hyperparathyroidism, $n = 4$; kidney transplant, $n = 45$; acute myocardial infarction, $n = 9$; acute heart failure, $n = 15$; serious infection, $n = 4$; wPTH levels higher than iPTH levels, $n = 14$; insufficient clinical data, $n = 90$). The remaining 773 patients were classified according to CKD stage based on estimated glomerular filtration rate (eGFR); CKD stage 1 and 2 (≥ 60 mL/min/1.73 m²),

stage 3 (30–59 mL/min/1.73 m²), stage 4 (15–29 mL/min/1.73 m²), and stage 5 (< 15 mL/min/1.73 m²). In the medical record, a history of diabetes mellitus (DM), coronary artery disease (CAD), chronic heart failure (CHF), hypertension (HTN), and hyperlipidemia (HL) were collected. CAD was defined as disease which causes occlusion or stenosis of the coronary arteries, such as myocardial infarction and angina pectoris. CHF was defined as chronic cardiac disorder which causes lowering exercise tolerance with dyspnea, malaise, and edema. HTN was defined as ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic pressure and/or antihypertensive agents treatment. HL was defined as LDL cholesterol ≥ 140 mg/dL, HDL cholesterol ≤ 40 mg/dL, and/or triglyceride ≥ 150 mg/dL and/or lipid-lowering agents treatment. Among the patients with all CKD stages, 206 were able to follow the composite renal outcome (kidney transplantation, dialysis, and 30% decline in eGFR) in the two years retrospectively based on medical records.

Laboratory measurements

Laboratory tests were conducted using standardized clinical laboratory methods. The remaining EDTA–2Na plasma samples were stored at -80 °C until analysis. iPTH and wPTH levels were determined using the Elecsys Intact PTH assay and Elecsys PTH (1–84) assay (Roche Diagnostics K.K., Tokyo, Japan).

Statistical analysis

Computer software application IBM SPSS statistics version 25.0 (SPSS Inc., IL, USA) was used for all statistical analyses. Normally distributed variables were presented as mean values \pm standard deviation, while non-normally distributed variables were presented as median (quartile). Each group was compared using linear by linear analysis for nominal variables and Jonckheere–Terpstra analysis and analysis of variance for continuous variables. We used locally weighted scatter plot smoothing (LOWESS) curve on the scatter diagram of the w/i PTH ratio, the iPTH, the wPTH, corrected calcium, and phosphate levels versus eGFR and estimated the eGFR threshold value at which the slope of the w/i PTH ratio, the iPTH, the wPTH, serum calcium, and phosphate levels became steeper by minimizing the residual sum of squares. Simple linear regression analysis was performed on wPTH and iPTH in patients with each CKD stage. To determine independent predictors of the w/i PTH ratio, multiple linear regression analysis was conducted. The relationship between the composite renal outcome and w/i PTH ratio was investigated using Kaplan–Meier curves and Cox proportional hazard analysis. A P value of < 0.05 was considered statistically significant.

Results

Patient characteristics

Table 1 shows the characteristics and laboratory data for all patients according to each CKD stage. Although patients were significantly older as CKD stage progressed, no statistical difference was observed between the CKD stage 4 and 5 group. No differences in the percentage of males, smoking history, DM, and HL were observed among the study groups. The number of patients with

CAD, CHF, and HTN increased significantly with declining kidney function. Increased prescription of calcium carbonate and decreased prescription of bisphosphonate were observed as CKD stage progressed. Laboratory data showed that as CKD stage progressed, iPTH, wPTH, blood urea nitrogen, creatinine, C-reactive protein, and urinary protein levels increased, while the w/i PTH ratio, hemoglobin, eGFR, and total cholesterol levels decreased. The CKD stage 5 group had significantly lower serum calcium levels and significantly higher serum phosphate levels than the other CKD groups.

Table 1 Patient characteristics and laboratory data

| | Stages 1–5 | Stage 1/2 | Stage 3 | Stage 4 | Stage 5 | <i>P</i> value |
|-----------------------------------|--------------------|------------------|-------------------|--------------------|---------------------|----------------|
| N | 773 | 92 | 233 | 217 | 231 | |
| <i>Characteristics</i> | | | | | | |
| Age (years) | 63 ± 17 | 50 ± 19 | 60 ± 17 | 67 ± 16 | 68 ± 10 | <0.001 |
| Male gender (%) | 518 (67) | 57 (62) | 151 (65) | 158 (73) | 152 (66) | 0.29 |
| Smoking (%) | 342 (44) | 27 (29) | 108 (46) | 107 (49) | 100 (43) | 0.20 |
| History of DM (%) | 247 (32) | 35 (38) | 78 (33) | 48 (22) | 86 (37) | 0.55 |
| History of CAD (%) | 110 (14) | 3 (3) | 29 (12) | 34 (16) | 44 (19) | <0.001 |
| History of CHF (%) | 69 (9) | 1 (1) | 16 (7) | 36 (17) | 16 (7) | 0.009 |
| History of HTN (%) | 675 (87) | 58 (63) | 202 (87) | 197 (91) | 218 (94) | <0.001 |
| History of HL (%) | 413 (53) | 44 (48) | 132 (57) | 96 (44) | 141 (61) | 0.17 |
| <i>Medication</i> | | | | | | |
| Statin (%) | 370 (48) | 32 (35) | 119 (51) | 79 (36) | 140 (61) | 0.001 |
| Calcium carbonate (%) | 42 (5) | 0 (0) | 6 (3) | 3 (1) | 33 (14) | <0.001 |
| Active vitamin D (%) | 103 (13) | 13 (14) | 24 (10) | 35 (16) | 31 (13) | 0.64 |
| Bisphosphonate (%) | 106 (14) | 30 (33) | 21 (9) | 36 (17) | 19 (8) | <0.001 |
| <i>Laboratory data</i> | | | | | | |
| Hb (g/dL) | 11.5 ± 1.9 | 13.3 ± 1.8 | 12.4 ± 1.6 | 11.1 ± 1.6 | 10.2 ± 1.3 | <0.001 |
| TP (g/dL) | 6.88 ± 0.82 | 6.55 ± 0.99 | 7.16 ± 0.49 | 7.01 ± 0.61 | 6.61 ± 0.82 | 0.10 |
| Alb (g/dL) | 3.81 ± 0.67 | 3.84 ± 0.92 | 3.84 ± 0.73 | 3.93 ± 0.49 | 3.67 ± 0.60 | <0.001 |
| BUN (mg/dL) | 40.2 ± 24.1 | 14.9 ± 4.6 | 25.2 ± 12.4 | 40.0 ± 11.3 | 65.2 ± 23.2 | <0.001 |
| Cr (mg/dL) | 2.03 (1.29–3.62) | 0.75 (0.66–0.88) | 1.33 (1.11–1.56) | 2.24 (1.92–2.71) | 5.05 (3.84–6.49) | <0.001 |
| eGFR (mL/min/1.73m ²) | 30.8 ± 23.1 | 79.4 ± 14.5 | 41.7 ± 8.9 | 22.1 ± 4.0 | 9.2 ± 3.1 | <0.001 |
| cCa (mg/dL) | 9.24 ± 0.61 | 9.58 ± 0.39 | 9.48 ± 0.39 | 9.29 ± 0.33 | 8.84 ± 0.81 | <0.001 |
| P (mg/dL) | 3.80 ± 0.95 | 3.50 ± 0.53 | 3.39 ± 0.49 | 3.45 ± 0.58 | 4.65 ± 1.13 | <0.001 |
| TC (mg/dL) | 185.7 ± 55.3 | 227.9 ± 85.0 | 189.9 ± 58.3 | 177.3 ± 34.3 | 172.6 ± 43.5 | <0.001 |
| ALP (U/L) | 251.4 ± 101.7 | 198.6 ± 60.9 | 241.2 ± 83.5 | 263.2 ± 116.6 | 271.0 ± 108.4 | <0.001 |
| CRP (mg/dL) | 0.07 (0.03–0.27) | 0.04 (0.03–0.11) | 0.06 (0.03–0.19) | 0.08 (0.03–0.34) | 0.10 (0.03–0.37) | <0.001 |
| HbA1c (%) | 5.80 (5.50–6.20) | 5.85 (5.50–7.08) | 5.90 (5.70–6.40) | 5.80 (5.50–6.10) | 5.80 (5.30–6.10) | 0.73 |
| iPTH (pg/mL) | 105.5 (66.8–177.6) | 49.1 (33.7–70.7) | 70.1 (53.0–100.1) | 113.8 (83.0–150.1) | 240.8 (161.7–370.6) | <0.001 |
| wPTH (pg/mL) | 80.9 (53.2–126.2) | 43.5 (30.1–60.2) | 58.9 (44.7–81.4) | 90.6 (64.2–115.6) | 174.2 (121.4–243.1) | <0.001 |
| w/i PTH ratio | 0.78 ± 0.07 | 0.85 ± 0.06 | 0.81 ± 0.06 | 0.78 ± 0.05 | 0.59 ± 0.27 | <0.001 |
| Urinary protein (g/g•Cr) | 0.83 (0.21–2.53) | 0.29 (0.14–1.79) | 0.42 (0.13–1.79) | 0.51 (0.20–1.62) | 2.12 (0.90–4.54) | <0.001 |

DM diabetes mellitus, CAD coronary artery disease, CHF chronic heart failure, HTN hypertension, HL hyperlipidemia, Hb hemoglobin, TP total protein, Alb albumin, BUN blood urea nitrogen, Cr creatinine, eGFR estimate glomerular filtration rate, cCa corrected calcium, P phosphate, TC total cholesterol, ALP alkaline phosphatase, CRP C-reactive protein, HbA1c hemoglobin A1c, iPTH intact parathyroid hormone, wPTH whole parathyroid hormone, w/i PTH wPTH/iPTH

Correlation between eGFR and w/i PTH ratio, serum calcium, and serum phosphate levels

Simple linear regression analysis showed that the w/i PTH ratio was significantly correlated with eGFR in patients with CKD stage 1–5 ($r=0.675$; $P<0.001$). At an eGFR

of 24.1 mL/min/1.73 m², the slope of the LOWESS curve on the w/i PTH ratio versus eGFR scatter plot steepened. Similarly, the slope of the LOWESS curves on the iPTH, the wPTH, serum calcium, and serum phosphate levels versus eGFR scatter plot steepened at an eGFR of 17.5, 17.5, 20.0 and 17.8 mL/min/1.73 m², respectively (Fig. 1). Simple

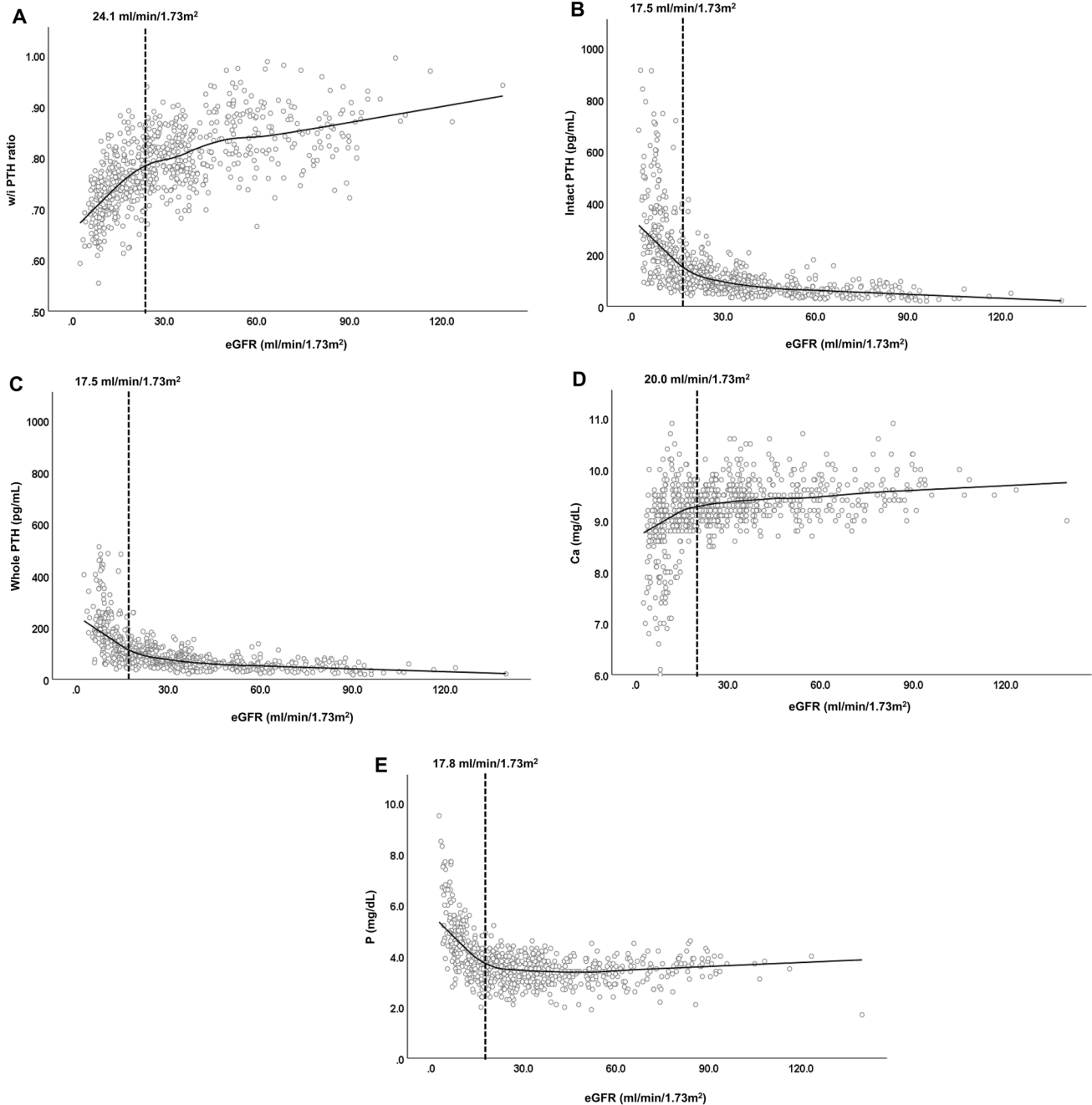


Fig. 1 Scatter diagram with LOWESS curve of the association between eGFR and w/i PTH ratio (a), iPTH (b), wPTH (c), serum calcium levels (d), and serum phosphate levels (e) among predialysis CKD patients. LOWESS, locally weighted scatter plot smoothing; eGFR, estimated glomerular filtration rate; w/i PTH, whole/

intact parathyroid hormone; wPTH, whole PTH; iPTH, intact PTH; CKD, chronic kidney disease. The dashed lines represent statistical thresholds for eGFR (a 24.1 mL/min/1.73 m², b 17.5 mL/min/1.73 m², c 17.5 mL/min/1.73 m², d 20.0 mL/min/1.73 m², and e 17.8 mL/min/1.73 m²) at which the slopes steepened, respectively

linear regression analysis showed a significantly strong correlation between iPTH and wPTH in patients at each CKD stage (Stage 1/2: $r=0.985$; $P<0.001$, Stage 3: $r=0.986$; $P<0.001$, Stage 4: $r=0.990$; $P<0.001$, Stage 5: $r=0.994$; $P<0.001$) (Fig. 2).

Correlation between clinical factors and w/i PTH ratio

Multivariate analysis showed that the w/i PTH ratio was significantly associated with male gender and use of active vitamin D agents among those with CKD stage 1 and 2; age, serum albumin levels, and eGFR among those with CKD stage 3; age, male gender, and eGFR among those with CKD stage 4; and use of active vitamin D agents, serum calcium, alkaline phosphatase levels and eGFR among those with CKD stage 5 (Table 2).

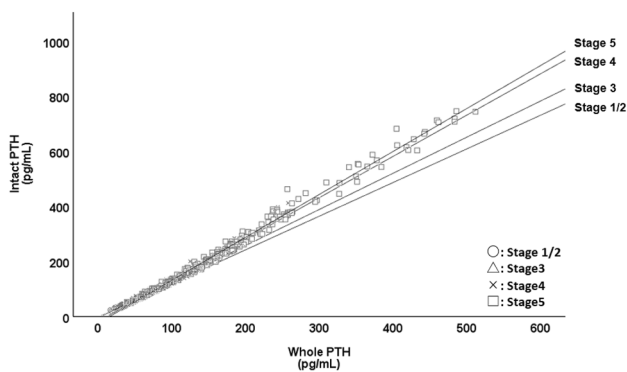


Fig. 2 Relationship between whole PTH and intact PTH levels among patients with each CKD stage. PTH, parathyroid hormone; CKD, chronic kidney disease. Intact PTH levels were strongly correlated with whole PTH levels at each CKD stage (Stage 1/2: $r=0.985$; $P<0.001$, Stage 3: $r=0.986$; $P<0.001$, Stage 4: $r=0.990$; $P<0.001$, Stage 5: $r=0.994$; $P<0.001$)

Predicting renal events using the w/i PTH ratio

A total of 206 patients with all CKD stages had available data on the composite renal outcome based on medical records and were divided into two groups based on whether or not their w/i PTH ratio was greater than or equal to the median value 0.79 among these patients. Total 66 composite renal outcomes were observed in the two years; 3 were kidney transplantation, 31 were dialysis initiation, and 32 were 30% decline in eGFR. The mean follow-up duration was 83.2 ± 33.3 weeks. The Kaplan–Meier curve showed that patients with a w/i PTH ratio of more than 0.79 had significantly better 2-year composite renal outcome compared to those with a lower w/i PTH ratio. The event free survival rate in the w/i PTH ratio >0.79 and ≤ 0.79 group was 87% and 50%, respectively (Fig. 3). Multivariate analysis based on the Cox proportional hazards model showed

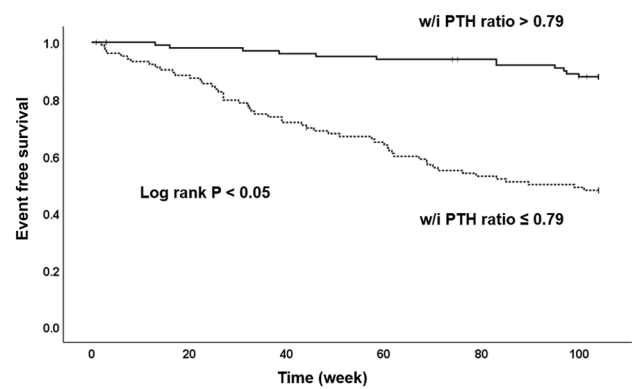


Fig. 3 Kaplan–Meier survival curve showing composite renal outcome according to the w/i PTH ratio. w/i PTH, whole/intact parathyroid hormone; CKD, chronic kidney disease. Predialysis CKD patients having a w/i PTH ratio ≤ 0.79 had significantly worse composite renal outcome compared to those having the w/i PTH ratio >0.79 (Log–rank, $P<0.05$)

Table 2 Correlation between whole/intact PTH ratio and clinical factors (multivariate analysis)

| | Stages 1–5 | Stage 1/2 | Stage 3 | Stage 4 | Stage 5 |
|-------------------------|----------------------|--------------------|--------------------|----------------------|----------------------|
| Age | 0.228 [‡] | – 0.005 | 0.361 [‡] | 0.259 [‡] | 0.135 |
| Male gender | 0.126 [‡] | 0.303 [‡] | 0.121 | – 0.219 [‡] | 0.106 |
| Diabetes mellitus | – 0.004 | 0.020 | – 0.006 | 0.068 | – 0.106 |
| Active vitamin D agents | – 0.011 | 0.460 [‡] | 0.085 | – 0.105 | – 0.189 [‡] |
| Hb | 0.016 | 0.017 | – 0.039 | 0.058 | 0.029 |
| Alb | 0.106 [‡] | 0.243 | 0.166 [‡] | – 0.027 | 0.037 |
| cCa | 0.148 [‡] | 0.254 | – 0.028 | 0.108 | 0.251 [‡] |
| P | – 0.099 [‡] | – 0.049 | 0.128 | 0.027 | – 0.023 |
| ALP | – 0.068 [‡] | – 0.146 | – 0.021 | – 0.042 | – 0.216 [‡] |
| eGFR | – 0.604 [‡] | 0.198 | 0.345 [‡] | 0.317 [‡] | 0.362 [‡] |

PTH parathyroid hormone, Hb hemoglobin, Alb albumin, cCa corrected calcium, P, phosphate, ALP alkaline phosphatase, eGFR estimate glomerular filtration rate

[‡] $P<0.05$

that serum phosphate levels (HR 1.61, 95% CI 1.07–2.41; $P < 0.05$), eGFR (HR 0.92, 95% CI 0.90–0.96; $P < 0.05$), urinary protein/creatinine ratio (HR 1.18, 95% CI 1.11–1.26; $P < 0.05$), and w/i PTH ratio [hazard ratio (HR) 0.004, 95% CI 0.00002–0.96; $P < 0.05$], were statistically significant predictors for the composite renal outcome (Table 3).

Discussion

The present study demonstrated that (1) the w/i PTH ratio decreased as kidney function declined and rapidly decreased when eGFR reduced to less than 24.1 mL/min/1.73 m²; (2) serum calcium levels rapidly decreased and serum phosphate levels rapidly increased when eGFR reduced to less than 20.0 and 17.8 mL/min/1.73 m², respectively; and (3) a lower w/i PTH ratio was significantly associated with poor renal outcome.

PTH is among the chronic kidney disease–mineral bone disorder (CKD–MBD) parameters that need to be controlled appropriately [5]. Serum PTH levels are elevated to keep normal active vitamin D and calcium levels within normal range. Impaired excretion of phosphate from urine due to reduced kidney function and resistance to the action of PTH under uremic conditions also increase serum PTH levels [15]. Thus, PTH has a close interaction with calcium and phosphate metabolism and greatly affects mineral and bone balance. The present study showed that the w/i PTH ratio decreased rapidly when eGFR was below 24.1 mL/min/1.73 m². Therefore, from CKD stage 4, the balance between wPTH and iPTH seems to change. Previous studies have demonstrated that the prevalence of patients with hyperphosphatemia and hypocalcemia increased progressively in those with CKD stage 4 and 5 [16, 17]. The results of our study also showed that serum phosphate and calcium levels steeply changed around CKD stage 4 and that the w/i

PTH ratio changed followed by serum calcium and phosphate levels.

A decrease in serum calcium levels, increase in serum phosphate levels, and impaired excretion from kidney due to declining kidney function led to an increase in 7–84 PTH. Although 1–84 PTH has a physiologically active property, 7–84 PTH binds to the PTH receptor and inhibits 1–84 PTH activity [7]. In addition, a previous experimental study demonstrated that 7–84 PTH induced hypocalcemia and inhibited the 1–84 PTH secretory response to hypocalcemia [8]. Furthermore, parathyroid cells predominantly secrete 7–84 PTH during hypercalcemia, whereas 1–84 PTH secretion is promoted during hypocalcemia [18, 19]. The progression of CKD impairs the excretion of 1–84 PTH and 7–84 PTH fragments from the kidney. Therefore, the increase in both 1–84 PTH and 7–84 PTH levels and the change in the balance between 1–84 PTH and 7–84 PTH results in a lower w/i PTH ratio during advanced CKD. Furthermore, our multivariate analysis showed that serum phosphate level was not a significant predictor of the w/i PTH ratio at all CKD stages, while serum calcium level was a significant predictor of the w/i PTH ratio only at CKD stage 5. Taken together, our results suggest that serum calcium level has a stronger effect on increasing PTH production compared to serum phosphate level.

A few reports have examined the clinical implication of the w/i PTH ratio in clinical settings. A previous study including predialysis Japanese patients with CKD demonstrated that the w/i PTH ratio increased with serum calcium level and GFR decline and was significantly associated with bone metabolic markers [20]. Another study performing bone biopsy reported that the w/i PTH ratio was a useful predictor of bone turnover in patients undergoing dialysis [21]. Moreover, the aforementioned study revealed that a lower w/i PTH ratio (< 1) was associated with low bone turnover. A few studies have also shown that the w/i PTH ratio was associated with hyperparathyroidism severity [22, 23]. Thus, although all previous studies had focused on the relationship between the w/i PTH ratio and bone turnover or hyperparathyroidism, no study to date has examined the relationship between the w/i PTH ratio and renal outcome. The present study showed that the w/i PTH ratio was an independent and significant predictor for composite renal outcome after adjustment for several factors, including kidney function, serum calcium levels, and serum phosphate levels in predialysis CKD patients. Therefore, we believe that the results presented herein are of considerable value.

Several possible mechanisms can explain the poor renal outcome observed with a low w/i PTH ratio. As mentioned above, a decrease in the w/i PTH ratio reflects an increase in the 7–84 PTH fragment. Previous experimental studies have demonstrated that the 7–84 fragment decreased phosphate excretion from urine and inhibits the conversion of 25(OH)

Table 3 Multivariate Cox regression analysis for composite renal outcome

| | Hazard ratio | 95% CI | <i>P</i> value |
|----------------------------------|--------------|-----------|----------------|
| Age | 0.99 | 0.97–1.01 | 0.09 |
| Smoking | 0.73 | 0.44–1.20 | 0.21 |
| Diabetes mellitus | 1.15 | 0.67–1.96 | 0.62 |
| cCa | 0.89 | 0.58–1.37 | 0.60 |
| P | 1.61 | 1.07–2.41 | < 0.05 |
| eGFR | 0.92 | 0.90–0.96 | < 0.05 |
| Urinary protein/creatinine ratio | 1.18 | 1.11–1.26 | < 0.05 |
| w/i PTH ratio (0.1 increase) | 0.58 | 0.33–0.99 | < 0.05 |

cCa corrected calcium, *P* phosphate, eGFR estimate glomerular filtration rate, w/i PTH whole/intact parathyroid hormone

vitamin D to 1, 25(OH)₂ vitamin D [7, 24]. These physiological alterations may increase FGF23 and decrease klotho. In addition, reduced 1, 25(OH)₂ vitamin D activates the renin–angiotensin–aldosterone system [25]. These changes in mineral bone metabolisms could affect the progression of kidney damage [26–28].

Some limitations of the present study are worth noting. Firstly, given the observational nature of this study, the associations between several factors and the w/i PTH ratio may not reflect direct effects. Furthermore, this study used the serum calcium level calculated using Payne's equation. Therefore, there may be a slight dissociation from the ionized calcium level described previously [29]. Secondly, as we used second- and third-generation parathyroid hormone assays, we could not measure oxidized and non-oxidized PTH separately. It has been reported that higher non-oxidized PTH reduced the odds ratio for death in hemodialysis patients [30]. If we also could measure these types of PTH, we may obtain further information. Thirdly, we could not measure serum 25(OH) vitamin D, 1, 25(OH)₂ vitamin D, and FGF23 levels and determine their effects on the w/i PTH ratio. Future studies should therefore investigate whether such factors influence the w/i PTH ratio and renal outcome.

In conclusion, our data suggest that the w/i PTH ratio decreases as kidney function declines possibly due to disorders in PTH fragment excretion from the kidney and calcium/phosphate metabolism. Furthermore, a lower w/i PTH ratio might be associated with worse renal outcome.

Acknowledgements The authors thank the staff of Kobe University Graduate School of Medicine (Dr Shuhei Watanabe, Dr Kimihiko Goto, and Dr Nozomi Yamada).

Author contributions FH drafted this study. KO analyzed the data and wrote the text. All co-authors reviewed and approved this paper.

Funding None.

Compliance with ethical standards

Conflict of interest This study was partly supported by Roche Diagnostics K.K.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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