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ORIGINAL ARTICLE

Low parathyroid hormone levels after parathyroidectomy reduce cardiovascular mortality in chronic hemodialysis patients

Noriyuki Iwamoto[1] · Nodoka Sato[1] · Masaya Nishida[1] · Tetsuya Hashimoto[1] · Hiroyuki Kobayashi[1] · Satoru Yamazaki[1] · Koji Okino[1] · Masato Nishimura[1] · Toru Takatani[1] · Yu Okamoto[1] · Tsuneyuki Nakanouchi[2] · Masaki Koyama[3] · Naoto Adachi[4] · Kanji Ninomiya[4] · Hisao Mabuchi[4] · Kunitoshi Iseki[5]

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Abstract

Background The aim of the study is to elucidate whether parathyroid hormone (PTH) levels after parathyroidectomy affect the prognosis of patients with secondary hyperparathyroidism.

Subjects and methods Two hundred and ninety-five patients, who underwent PTx without autotransplantation from July 1998 to December 2011, were divided into the low ($n = 148$) and high ($n = 147$) PTH groups, using the median value of each mean value of intact PTH after surgery (16.6 pg/mL). After observation for 5.00 years, we evaluated demographic factors, influences of postoperative mineral metabolism, magnitude of uremia, and vitamin D receptor activators on their prognosis, with the multivariate Cox proportional hazard model.

Results While overall survival rates in the high and low PTH groups were 54.9 and 74.2 %, respectively ($P = 0.1500$), cardiovascular survival rates were 71.6 and 94.4 %, respectively ($P = 0.0256$). The hazard ratio for cardiovascular mortality in the high PTH group (≥16.6 pg/mL) was 3.132 ($P = 0.0470$), and those in groups with the median age more than 59 years and with cardiovascular disease were 2.654 ($P = 0.0589$) and 3.377 ($P = 0.0317$), respectively. The intact PTH level 6 days after surgery and the mean postoperative intact PTH value showed a strong correlation (Spearman $\rho = 0.9007$, $P < 0.0001$, $y = 0.4725x + 30.395$, $R^2 = 0.51798$).

Conclusion The present study suggests that maintaining low PTH levels after parathyroidectomy reduces cardiovascular mortality and improves the prognosis. Total parathyroidectomy (more than 4 glands) without autotransplantation seems to be one of the treatment options for managing severe secondary hyperparathyroidism.

Keywords Secondary hyperparathyroidism · Parathyroidectomy · PTH · Cardiovascular mortality

Introduction

Secondary hyperparathyroidism (SHPT) is a major complication in hemodialysis patients, which is closely associated with their survival [1, 2]. In 2006, Kidney Disease/Improving Global Outcomes (KDIGO) presented new concepts of renal osteodystrophy to cover chronic kidney disease-mineral and bone disorders (CKD-MBD) [3], and the concepts were later presented as clinical practice guidelines [4]. In Japan, guidelines on CKD-MBD were concurrently presented in 2009 [5] and revised later. Although these guidelines recommend target values for management of bone mineral metabolism, there is no standard on parathyroid hormone (PTH) values. Hence, target values for PTH vary widely among guidelines [4, 5].

Various symptoms in patients with advanced SHPT have been demonstrated to be alleviated after parathyroidectomy (PTx) [6–9]. Their prognosis after PTx is shown to be better than that of patients received conservative treatments with active vitamin D receptor activators

✉ Noriyuki Iwamoto
iwamoto@tojinkai.jp

[1] Urology Division, Tojinkai Hospital, 83-1, Iga, Momoyama-cho, Fushimi-ku, Kyoto 612-8026, Japan

[2] Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan

[3] Nishijin Hospital, Kyoto, Japan

[4] Mabuchi Clinic, Kyoto, Japan

[5] Dialysis Unit, University of the Ryukyus Hospital, Okinawa, Japan

(VDRAs) [10–14]. However, there are few reports on the relationship between PTH levels and the prognosis after PTx [15]. In this study, we retrospectively evaluated the prognosis of patients after PTx by dividing them into two groups, according to the median value of individual mean values of the postoperative PTH level.

Subjects and methods

Subjects

Three hundred and three patients on hemodialysis (3 times a week, 4–6 h per session), who had no history of either kidney transplantation or treatments with cinacalcet, underwent PTx without autotransplantation from July 1998 to the end of 2011. Among these 303 patients, 295 patients with the follow-up data were enrolled in this study. The observation period was 5.00 ± 0.28 years (mean ± standard deviation, SD), and the maximum observation period was 12 years after PTx. Based on the data obtained every 4–8 weeks during the observation period, the mean value of intact PTH (iPTH) was calculated to be 65.0 ± 104.4 pg/mL, and the mean number of measurements was 47.7 ± 34.8/patient.

Patients were allocated to one of the two groups, the low PTH (iPTH < 16.6 pg/mL) ($n = 148$) and high PTH (PTH ≥ 16.6 pg/mL) ($n = 147$) groups, using the median iPTH value of 16.6 pg/mL. Then, their background at PTx, postoperative PTH profile, mineral parameters, magnitude of uremia [anemia, blood urea nitrogen (BUN), creatinine, lipids, and C-reactive protein (CRP)], and VDRAs on the prognosis were examined. Continuous variables were dichotomized at the median value and used as prognostic factors. The primary endpoint was cardiovascular death and the secondary endpoint was overall mortality. Cardiovascular death included death due to cerebral infarction/hemorrhage, subarachnoid hemorrhage, myocardial infarction, and heart failure, as well as sudden death. PTx was performed under general anesthesia, and visible parathyroid glands were extirpated as completely as possible. The number of extirpated glands was 4 or more in 221 patients, and 3 or fewer in 74 patients. Based on laboratory findings obtained every 2 weeks, doses of VDRAs, phosphate binders, and erythropoietin stimulating agents were determined, using target ranges as below; $3.5 \leq$ phosphorus < 6.0 mg/dL, $8.0 \leq$ calcium < 9.5 mg/dL, and $10.0 \leq$ hemoglobin < 12.0 g/dL.

Data collection

Blood samples were collected at the beginning of the first hemodialysis of the week. Mean values were based on the data obtained every 4 weeks for serum levels of calcium, phosphorus, albumin, alkaline phosphatase (ALP), hemoglobin, BUN, creatinine, and CRP. Mean values were calculated with the data obtained every 4–8 weeks for iPTH and every 1–6 months for total cholesterol (T-CHO), high-density lipoprotein cholesterol (HDL-C), and triglycerides, respectively. The iPTH level was analyzed by an immunoradiometric assay from the start of the study to March 2003, and the method was changed to an electrochemiluminescence immunoassay from April 2003. As a routine screening examination before surgery, 12-lead electrocardiogram (ECG) was checked, and a cardiologist diagnosed abnormal findings on the ECG, such as left ventricular hypertrophy, abnormal Q waves, inverted T waves, nonspecific and specific ST changes, arrhythmias, and conduction disturbances.

Statistical analysis

All results were expressed as the mean ± SD. The unpaired t test was used for analysis of continuous variables, while the Fisher's exact test was used for categorical data. The Kaplan–Meier method was employed to calculate survival rates, and the log-rank test was performed to assess the significance of differences in survival. The multivariate analysis of prognostic factors was performed using the Cox proportional hazard model. All tests were two-sided, and $P < 0.05$ was considered significant. Statistical analyses were performed with JMP Version 7.0 (SAS Institute Inc., Cary, NC, USA).

The Ethical Committee for Human Research of Tojinkai Hospital approved this study, and the study was performed in accordance with the Principles of the Declaration of Helsinki.

Results

Patient profiles at PTx are shown in Table 1. In the low PTH group, the incidence of cardiovascular complications and the frequency of abnormal ECG were significantly lower than those in the high PTH group. There were no differences between the two groups with regard to age, sex, dialysis history, diabetes, body mass index (BMI), Kt/v, antihypertensive therapy, and blood pressure at the time of surgery. In the low PTH group, serum calcium and albumin levels were significantly higher at the time of surgery, although there were no significant differences in other variables, such as serum iPTH and phosphorus values. 6 days after surgery, significantly lower iPTH levels were observed in the low PTH group (Table 2).

The data obtained after PTx are shown in Table 3. The low PTH group showed significantly lower serum calcium,

Table 1 Patients' profiles at parathyroidectomy

	Low PTH group iPTH < 16.6 pg/mL, $n = 148$		High PTH group iPTH ≥ 16.6 pg/mL, $n = 147$		
	n		*n*		*P*
Age (years)	148	58.3 ± 10.4	147	59.3 ± 10.8	0.4460
Sex (male), *n* (%)	148	79 (53.4)	147	76 (51.7)	0.7729
Dialysis vintage (months)	148	154.5 ± 68.7	147	158.4 ± 82.3	0.6559
Diabetes mellitus (+), *n* (%)	148	14 (9.5)	147	13 (8.9)	0.8548
Cardiovascular disease (+), *n* (%)	148	16 (10.8)	147	32 (21.8)[a]	0.0108
Cardiac disease (+), *n* (%)	148	8 (5.4)	147	14 (9.5)[a]	0.1782
Post PCI, *n*		3		9	
Post CABG, *n*		2		4	
Valvular disease, *n*		2		0	
Dilated myocardiopathy, *n*		1		1	
Stroke, *n* (%)	148	4 (2.7)	147	12 (8.5)[a]	0.0384
Intracerebral bleeding, *n*		1		3	
Cerebral infarction, *n*		2		8	
Subarachnoid hemorrhage, *n*		1		1	
Aortic aneurysm, *n* (%)	148	1 (0.7)	147	2 (1.4) [a]	0.5617
PAD, *n* (%)	148	3 (2.0)	147	4 (2.7)[a]	0.4094
Body mass index (kg/m^2)	136	21.0 ± 3.2	132	21.5 ± 3.8	0.2633
Kt/v (single-pool Kt/v)	76	1.7 ± 0.4	92	1.7 ± 0.4	0.3676
Antihypertensives (+), *n* (%)	131	71 (54.2)	135	79 (58.5)	0.4775
Systolic blood pressure (mmHg)	125	137.6 ± 20.9	130	138.5 ± 23.6	0.7486
Diastolic blood pressure (mmHg)	125	77.0 ± 12.0	130	72.0 ± 14.1	0.9926
Electrocardiogram (normal), *n* (%)	133	68 (51.1)	139	53 (38.1)	0.0031

PAD peripheral arterial disease, patients who underwent percutaneous intervention, bypass, or amputation, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting

[a] Cardiovascular complications are expressed as total numbers including overlap

phosphorus, iPTH, and T-CHO levels. The ALP level tended to be lower in the low PTH group, although the effect was not significant. There were no differences in serum levels of albumin, hemoglobin, creatinine, CRP, HDL-C, and triglycerides. No difference was found in the duration of VDRAs administration.

The rate of extirpation of more than 4 glands was 58.5 % in the high PTH group, which was significantly lower than that in the low PTH group (92.6 %, $P < 0.001$). Moreover, the mean value of PTH measured during the observation period was strongly correlated with the iPTH value measured 6 days after PTx (Spearman $\rho = 0.9007$, $P < 0.0001$, $y = 0.4725x + 30.395$, $R^2 = 0.51798$) (Fig. 1).

No patient died in the immediate postoperative period. During the observation period, 43 deaths were reported, comprising 17 deaths (11.5 %) in the low PTH group and 26 deaths (17.7 %) in the high PTH group ($P = 0.1313$). There were 17 cardiovascular deaths, including 4 cases (2.7 %) in the low PTH group and 13 cases (8.8 %) in the high PTH group ($P = 0.0236$). Overall survival did not differ significantly between the two groups ($P = 0.1500$). However, cardiovascular death-free survival rates in the low and high PTH groups were 94.4 and 71.6 %, respectively ($P = 0.0256$) (Fig. 2). In a multivariate adjusted model ($n = 295$, event = 17) for sex, age, history of cardiovascular disease (CVD), dialysis duration, iPTH, albumin, calcium, phosphorus, and ALP, major factors in the CVD mortality risk were age ≥ 59 years (hazard ratio, 2.654; 95 % CI 0.964–7.306; $P = 0.0589$), history of CVD (hazard ratio, 3.377; 95 % CI 1.112–10.254; $P = 0.0317$) and iPTH ≥ 16.6 pg/mL (hazard ratio, 3.132; 95 % CI 1.015–9.664; $P = 0.0470$) (Fig. 3).

Discussion

The influence of serum concentrations of phosphorus, calcium and PTH on mortality has been discussed independently. Despite their interdependency, disordered mineral metabolism has never been assessed in the context of all three parameters. Although high levels of phosphorus

Table 2 Laboratory findings at parathyroidectomy

	Low PTH group, $n = 148$ iPTH median < 16.6 pg/mL		High PTH group, $n = 147$ iPTH median ≥ 16.6 pg/mL		
	n		*n*		*P*
Calcium (mg/dL)	148	10.53 ± 0.72	147	10.35 ± 0.71	0.0325
Phosphorus (mg/dL)	148	5.60 ± 1.24	147	5.63 ± 1.36	0.8556
Albumin (g/dL)	148	4.02 ± 0.40	147	3.90 ± 0.40	0.0190
ALP (U/L)	148	483.0 ± 374.2	147	523.6 ± 403.1	0.3711
iPTH (pg/mL)	148	846.2 ± 400.9	147	898.8 ± 380.3	0.2495
iPTH6 (pg/mL)	148	4.78 ± 5.83	147	141.56 ± 203.31	<0.0001
Hemoglobin (g/dL)	85	10.46 ± 1.12	102	10.47 ± 1.21	0.9457
BUN (mg/dL)	85	60.63 ± 15.58	102	60.83 ± 19.19	0.9359
Creatinine (mg/dL)	85	11.31 ± 2.62	102	11.30 ± 2.53	0.9703
CRP (mg/dL)	83	0.22 ± 0.34	95	0.32 ± 0.54	0.1334
T-CHO (mg/dL)	48	159.42 ± 30.04	67	169.61 ± 39.83	0.1309
HDL-C (mg/dL)	38	50.16 ± 15.29	51	55.57 ± 18.68	0.1484
Triglycerides (mg/dL)	35	123.37 ± 68.41	51	135.27 ± 136.57	0.5958

Calcium values were corrected with each albumin value by Payne's equation

ALP alkaline phosphatase, *iPTH* intact parathyroid hormone, *iPTH6* intact parathyroid hormone 6 days after parathyroidectomy, *BUN* blood urea nitrogen, *CRP* C-reactive protein, *T-CHO* total cholesterol, *HDL-C* high-density lipoprotein cholesterol

Table 3 Laboratory findings during the observation period after parathyroidectomy and the dosing period of VDRAs

	Low PTH group, $n = 148$ iPTH median < 16.6 pg/mL		High PTH group, $n = 147$ iPTH median ≥ 16.6 pg/mL		
	n		*n*		*P*
Calcium (mg/dL)	148	8.80 ± 0.47	147	9.08 ± 0.53	<0.0001
Phosphorus (mg/dL)	148	4.77 ± 0.67	147	4.97 ± 0.75	0.0203
Albumin (g/dL)	148	3.85 ± 0.32	147	3.83 ± 0.32	0.5809
ALP (U/L)	148	252.94 ± 108.08	147	280.71 ± 148.63	0.0674
iPTH (pg/mL)	148	6.33 ± 3.58	147	123.78 ± 122.15	<0.0001
Hemoglobin (g/dL)	111	10.65 ± 0.96	115	10.84 ± 0.99	0.1603
BUN (mg/dL)	113	64.80 ± 9.97	118	63.19 ± 10.31	0.2295
Creatinine (mg/dL)	113	11.34 ± 2.17	118	11.62 ± 1.93	0.3018
CRP (mg/dL)	113	0.55 ± 0.77	120	0.41 ± 0.38	0.0916
T-CHO (mg/dL)	112	160.1 ± 27.5	120	172.0 ± 35.0	0.0044
HDL-C (mg/dL)	99	52.6 ± 15.9	111	51.8 ± 16.4	0.7164
Triglycerides (mg/dL)	99	124.9 ± 61.5	107	136.0 ± 94.7	0.3277
VDRAs (months)	124	42.5 ± 30.0	121	43.4 ± 30.8	0.8158

Calcium values were corrected with each albumin value by Payne's equation

ALP alkaline phosphatase, *iPTH* intact parathyroid hormone, *BUN* blood urea nitrogen; *CRP* C-reactive protein, *T-CHO* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *VDRAs* vitamin D receptor activators

and calcium in the high PTH group had been supposed to increase cardiovascular mortality, we found that postoperative serum concentrations of phosphorus and calcium were not significant, but iPTH median ≥ 16.6 pg/mL was a significant factor in cardiovascular death in the Cox proportional hazard model.

Amelioration of hypertension [6] and attenuation of cardiac hypertrophy after PTx have been reported [16]. Since fibroblast growth factor 23 (FGF23) facilitates hypertrophy of cardiomyocytes [17], the beneficial outcome found in the present study may be partly attributed to recovery of cardiac function caused by the decrease in the

FGF23 level after PTx [18, 19]. The coronary artery calcification is also alleviated or stable after PTx [20, 21]. Fetuin-A is an inhibitor of extraosseous calcification [22], and an inverse correlation between fetuin-A and iPTH levels after PTx is reported [23]. On the other hand, the circulating level of fetuin-mineral complex, which reflects extraosseous calcification stress, is shown to decrease after either PTx or treatments with cinacalcet [24]. These may all contribute to suppression of cardiovascular death associated with cardiac dysfunction and vascular calcification of the coronary artery. A study on the relationship between the vascular system and PTH showed that the number of vascular endothelial precursor cells increased in peripheral blood along with a decrease in the PTH level [25]. In another study, PTx improved coronary flow reserve in primary hyperparathyroidism [26]. These organic and functional improvements of the cardiovascular system following PTx may be involved in the postoperative reduction of cardiovascular mortality. In addition to the effect of PTx on the cardiovascular system, improvements in muscle strength, sleep, and cognitive ability after surgery [7–10] seem to improve activity of daily living and thus contribute to the prognosis.

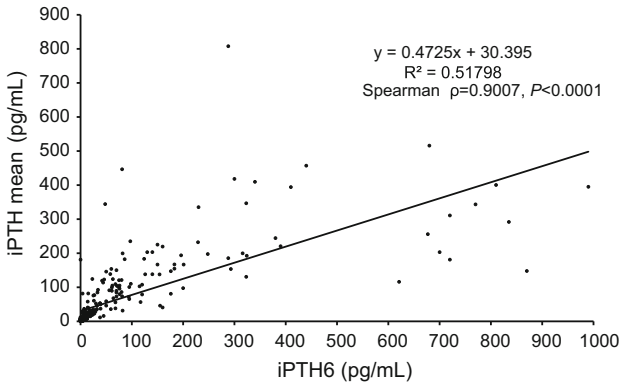

Fig. 1 Correlation between the serum level of iPTH measured 6 days after PTx (iPTH6) and the mean value of iPTH after surgery

Although suppression of the PTH level by PTx increases bone density, there is a risk of fracture associated with adynamic bone disease due to excess suppression of the PTH level. However, Rudser et al. found a clear decrease in the fracture rate after PTx, and they suggested that an increase in muscle strength and an improvement of activity of daily living contributed to prevention of fracture after PTx [27].

In 1993, we changed our surgical methods from subtotal PTx to total PTx with autotransplantation. However, the recurrence of hyperparathyroidism (iPTH $\geq$ 200 pg/mL) accompanied by high phosphorus levels was frequent (unpublished data). Thus, we changed again the surgical procedure to total PTx without autotransplantation in 1998. Complete excision of parathyroid glands is difficult, because of their variation among individuals, such as abnormal locations and existence of accessory glands [28]. Even in patients whom we deemed to have completed total PTx without autotransplantation, a minute amount of PTH could still be measured. This may be caused by another source of parathyroid hormone besides parathyroid glands, as shown in a mouse study [29]. For these reasons, total PTx (excision of more than 4 glands) without autotransplantation [30, 31] is judged to be a practical method for treating SHPT.

The ratio of extirpation of more than 4 glands was 58.5 % in the high PTH group, which was significantly

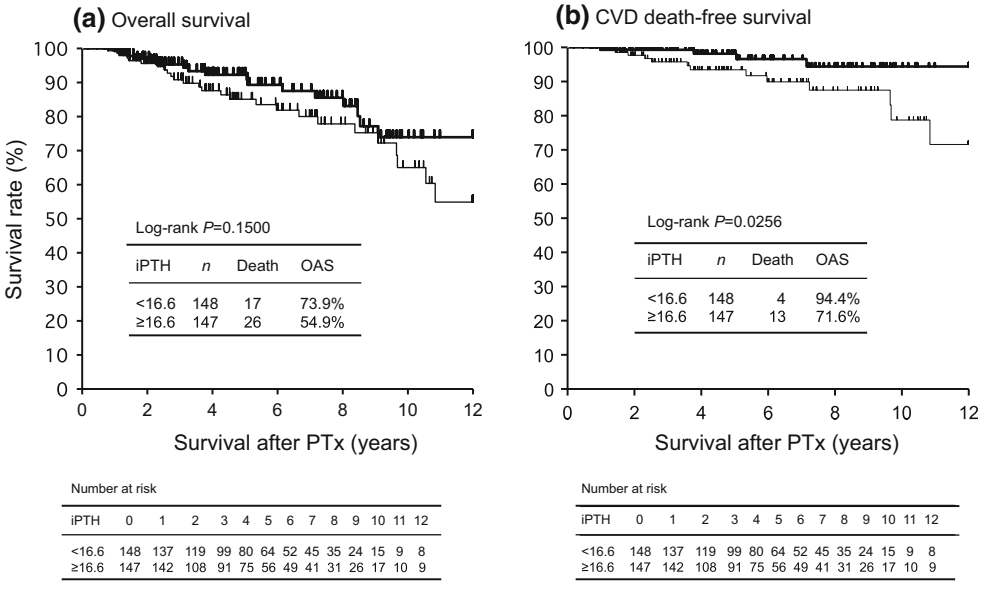

Fig. 2 Cumulative survival rates. **a** Overall survival and **b** cardiovascular disease (CVD) death-free survival. *Thick and thin lines* represent survival rates in the low and high PTH groups, respectively. *OAS* overall survival

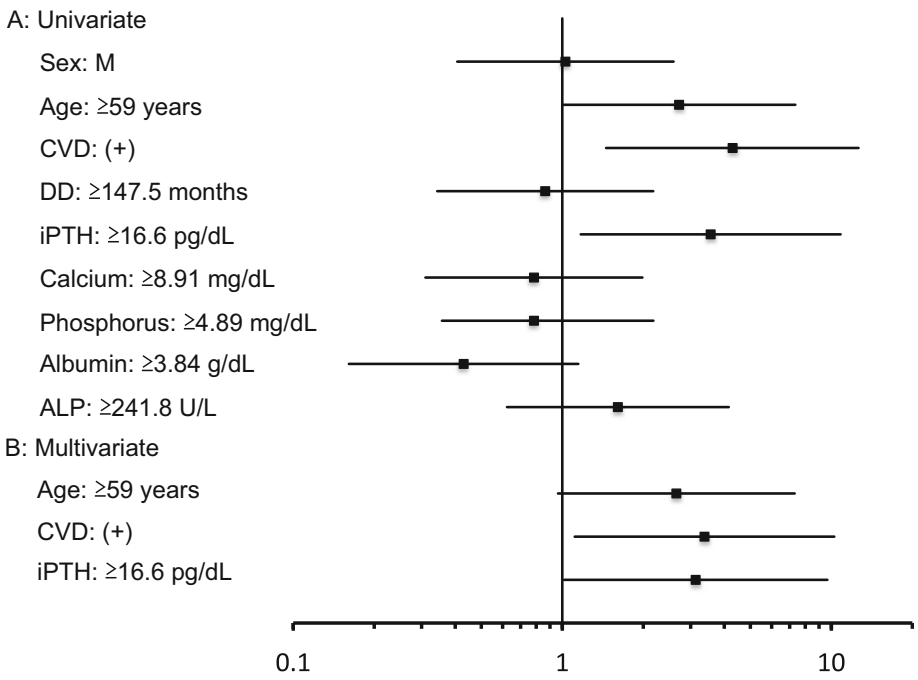

Fig. 3 Cox regression multivariate analyses for cardiovascular death using factors of $P < 0.20$, after univariate analyses using sex, age, history of cardiovascular disease (CVD), dialysis duration (DD), iPTH, albumin, calcium, phosphorus, and alkaline phosphatase, without a missing value ($n = 295$, 17 deaths). Calcium values were adjusted by Payne's equation

lower than that in the low PTH group (92.6 %, $P < 0.001$), and the iPTH day 6 and mean postoperative iPTH showed a strong correlation (Spearman $\rho = 0.9007$, $P < 0.0001$, $y = 0.4725x + 30.395$, $R^2 = 0.51798$). Therefore, the postoperative iPTH value seems to be sufficient to assess complete resection of the glands by PTx.

There are some limitations in the present study. First, the sample size was small, and the study was carried out retrospectively with a relatively short observation period of about 5 years. Second, this study did not clarify medications for patients suffering from cardiovascular disease and factors contributing to non-fatal cardiovascular disease. Third, VDRAs [32] and phosphate binders [33] could affect the prognosis, although they were not fully investigated. The low PTH group received very low doses of oral VDRAs (alfacalcidol 0.75–1.75 μg/week), while therapy in patients with persistently high PTH levels or postoperative recurrence (iPTH ≥ 200 pg/mL) was switched from oral administration of VDRAs to intravenous injections of VDRAs, concurrent administration of cinacalcet, or re-operation. Regarding phosphate binders, management of serum phosphorus has changed with release of non-calcium-containing binders (sevelamer hydrochloride in 2004 and lanthanum carbonate in 2009). Non-calcium-containing phosphate binders might have exerted an influence on the prognosis.

Despite various confounding factors, this study showed that the low PTH group had fewer cardiovascular deaths than the high PTH group. Further investigations on a large scale are required to clarify how the PTH level affects the prognosis after PTx and to define an optimal range of PTH.

Conclusion

The findings of the present study suggest the possibility that maintaining low PTH levels after PTx reduces cardiovascular mortality and improves the prognosis. Total PTx (more than 4 glands) without autotransplantation seems to be one of the options for managing severe SHPT.

Compliance with ethical standards

Financial support The authors declare that there is no financial support to disclose.

Conflict of interest The authors declare that there are no conflicts of interest to disclose.

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