Endocrine Journal 2014, **61** (7), 727-733

ORIGINAL

High serum parathyroid hormone and calcium are risk factors for hypertension in Japanese patients

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Abstract. Excess parathyroid hormone (PTH), known as primary hyperparathyroidism (pHPT), results in hypercalcemia and bone loss. Recent studies have shown that PTH is associated with the occurrence of hypertension in Western countries; however, controversy remains regarding high serum levels of PTH and calcium as risk factors for hypertension in Japanese patients. We retrospectively enrolled 114 consecutive Japanese patients who visited our hospital for examination and treatment of hypercalcemia and/or hypertension with serum calcium levels ≥9.8 mg/dL. To estimate the prevalence of hypertension, the patients were categorized according to calcium levels into hypercalcemic (10.2–13.4 mg/dL) and normocalcemic (9.8–10.1 mg/dL) groups, which were further categorized into high PTH (50–440 pg/mL) and low PTH (8–49 pg/mL) groups. The prevalence of hypertension was higher in patients with hypercalcemia than in patients with normocalcemia in both the high and low PTH groups. The prevalence of hypertension was higher in patients with high serum PTH levels than in patients with low serum PTH levels in both the hypercalcemic and normocalcemic groups. Logistic multiple regression analysis determined that serum calcium ($P < 0.05$) and PTH ($P < 0.01$) levels were positive contributors to hypertension. In conclusion, high serum levels of PTH and calcium are risk factors for hypertension in Japanese patients.

Key words: Parathyroid hormone, Calcium, Hypertension

PARATHYROID HORMONE (PTH) plays an important role in bone resorption and renal calcium reabsorption. Excess PTH, known as primary hyperparathyroidism (pHPT), results in hypercalcemia and bone loss [1] and is reported to be associated with high cardiovascular morbidity and mortality in both hypercalcemia-dependent and -independent manners [2-5]. Several studies have suggested that PTH levels are associated with hypertension and hypertension-related organ damage, including left ventricular hypertrophy and vascular stiffness [6-9]; however, controversy remains regarding serum levels of PTH and calcium as risk factors for hypertension. As almost all evidence has been obtained from Western countries [10-12], there are no available data regarding this controversy in Japanese patients.

The aim of this study was to determine if serum PTH and calcium levels are risk factors for hypertension in Japanese patients.

Materials and Methods

We retrospectively enrolled 114 consecutive Japanese patients who visited the endocrinology and metabolism or cardiology departments at Tokushima University Hospital between January 2004 and February 2013 for examination and treatment of hypercalcemia and/or hypertension. Because the aim was to assess the

Submitted Jan. 5, 2014; Accepted Apr. 23, 2014 as EJ14-0004
Released online in J-STAGE as advance publication May 22, 2014

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effects of PTH on hypertension, patients who had a measured and documented PTH level, with a corrected calcium level ≥9.8 mg/dL were included.

Hypertensive patients were defined as those with systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or individuals on antihypertensive medications. Exclusion criteria included critical conditions that could lead to a change in blood pressure profiles (i.e., active malignant diseases, sepsis) in addition to conditions that could result in hypercalcemia (*i.e*., vitamin D toxicity, tuberculosis, familial hypocalciuric hypercalcemia, malignancy-associated hypercalcemia).

Serum calcium levels were measured by the arsenazo III dye method using a commercial kit (Kainos Laboratories, Tokyo, Japan) and corrected according to serum albumin levels: corrected calcium (mg/dL) = total calcium (mg/dL) + (4 − albumin [g/dL]), when the serum albumin levels were <4 g/dL. In our hospital, the normal range for serum calcium was 8.8–10.1 mg/dL. Serum PTH levels were evaluated using intact PTH, which was measured with an electrochemiluminescence immunoassay at a commercially available laboratory (SRL, Tokyo, Japan).

For convenience of classification, we categorized the patients into hypercalcemic (10.2–13.4 mg/dL) and normocalcemic (9.8–10.1 mg/dL) groups and then divided each group further into high PTH (50–440 pg/mL) and low PTH (8–49 pg/mL) groups.

The prevalence of hypertension was calculated in each group and compared. The degrees of association between the prevalence of hypertension and the variables, including age, sex, body mass index (BMI), prevalence of diabetes mellitus hyperlipidemia, and pHPT, estimated glomerular filtration rate (eGFR), and serum levels of PTH and calcium, were assessed by logistic multiple regression analysis in all patients.

This study protocol was approved by the Tokushima University Hospital Ethics Committee.

Statistical analysis

Continuous variables were averaged and are expressed as the mean ± standard deviation or as a percentage for categorical parameters. Sex and the presence of hypertension, diabetes mellitus, and hyperlipidemia were coded as dummy variables.

Differences in clinical characteristics with/without hypertension and with/without pHPT were determined by Student t-tests or Chi-square tests. After stratification by serum calcium and PTH, differences in clinical characteristics were determined by one-way ANOVA. The prevalence of hypertension was compared using Chi-square tests. Single regression analysis was used to assess the correlations between serum calcium and PTH levels. Logistic multiple regression analysis was used to assess the degrees of association among variables with the prevalence of hypertension as the outcome variable. Paired t-tests were used to assess the change in blood pressure after parathyroidectomy.

All statistical analyses were performed using JMP 10 software. Statistical significance was defined as $P < 0.05$.

Results

Clinical characteristics of patients

The clinical characteristics of the patients enrolled in this study are summarized in Table 1. There were significant differences between patients with hypertension and those without hypertension in age, BMI, systolic and diastolic blood pressures, corrected and uncorrected calcium levels, serum PTH levels, eGFR, and presence of hyperlipidemia. None of the patients were taking vitamin D supplements, while 2 patients were taking diuretics (1 each, thiazide and loop diuretics). Statistical correction based on vitamin D supplementation and diuretic use did not affect the results.

The clinical characteristics of the 4 patient groups based on serum calcium and PTH levels are summarized in Table 2. There were significant differences between the 4 groups in age, systolic blood pressure, corrected and uncorrected serum calcium levels, and serum PTH levels.

PTH is closely associated with serum calcium levels

Single regression analysis determined that PTH levels were positively associated with serum calcium levels (Fig. 1).

High serum PTH and calcium levels are risk factors for hypertension

The prevalence of hypertension was higher in patients with hypercalcemia than in patients with normocalcemia (Fig. 2A), which was observed in both high and low PTH groups (Fig. 3).

The prevalence of hypertension was higher in patients with high serum PTH levels than in patients with low PTH levels (Fig. 2B), which was observed

Table 1 Clinical characteristics of the patients compared according to the presence of hypertension

Variables	Total	Hypertension (−)	Hypertension (+)	*P*-value
Number of patients	114	51 (44.7%)	63 (55.3%)	
Male	36 (31.6%)	17 (33.3%)	19 (30.2%)	0.31
Age (years)	56.7 ± 15.0	51.5 ± 15.8	60.8 ± 13.0	<0.001
Body mass index	23.5 ± 4.7	21.9 ± 4.7	24.6 ± 4.4	<0.001
Systolic BP (mmHg)	132.6 ± 18.9	122.7 ± 13.1	140.2 ± 19.3	<0.001
Diastolic BP (mmHg)	75.9 ± 13.6	72.3 ± 9.2	78.7 ± 15.6	0.02
Serum calcium (mg/dL)	10.5 ± 0.79	10.2 ± 0.48	10.8 ± 0.89	<0.001
Serum albumin (g/dL)	4.2 ± 0.4	4.2 ± 0.4	4.1 ± 0.4	0.38
Corrected serum calcium (mg/dL)	10.6 ± 0.8	10.2 ± 0.5	10.8 ± 0.9	<0.001
Serum PTH (pg/mL)	85.5 ± 76.7	56.1 ± 58.8	109.3 ± 81.4	<0.001
eGFR (mL/min/1.73m^2)	73.5 ± 23.2	82.0 ± 21.3	66.6 ± 22.6	<0.001
Complications				
Diabetes mellitus	36 (31.6%)	12 (23.5%)	24 (38.1%)	0.10
Hyperlipidemia	48 (42.1%)	10 (19.6%)	38 (60.3%)	<0.001

BP, blood pressure; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate

Table 2 Clinical characteristics of the patients according to the combination of serum calcium and parathyroid hormone levels

Variables	Normocalcemia Low PTH	Normocalcemia High PTH	Hypercalcemia Low PTH	Hypercalcemia High PTH	*P*-value
Number of patients	33 (28.9%)	15 (13.2%)	17 (14.9%)	49 (43.0%)	-
Male	14 (42.4%)	3 (20.0%)	9 (52.9%)	10 (20.4%)	-
Age (years)	51.5 ± 14.1	55.7 ± 16.4	54.2 ± 19.8	61.3 ± 12.1	0.03
Body mass index	23.1 ± 5.7	24.0 ± 6.5	23.3 ± 4.8	23.7 ± 3.6	0.92
Systolic BP (mmHg)	124.4 ± 14.0	130.3 ± 12.9	128.3 ± 19.4	139.8 ± 20.6	0.003
Diastolic BP (mmHg)	74.8 ± 11.0	72.9 ± 9.4	78.6 ± 11.1	76.6 ± 16.5	0.66
Serum calcium (mg/dL)	9.9 ± 0.1	9.9 ± 0.1	10.3 ± 0.2	11.2 ± 0.8	<0.001
Serum albumin (g/dL)	4.3 ± 0.3	4.3 ± 0.4	4.1 ± 0.6	4.1 ± 0.4	0.099
Corrected serum calcium (mg/dL)	9.9 ± 0.1	10.0 ± 0.1	10.4 ± 0.2	11.3 ± 0.8	<0.001
Serum PTH (pg/mL)	28.0 ± 9.0	85.4 ± 43.4	33.1 ± 12.5	142.5 ± 81.4	<0.001
eGFR(mL/min/1.73m^2)	77.0 ± 19.6	77.1 ± 29.3	73.1 ± 23.0	70.1 ± 23.7	0.54
Complications					
Diabetes mellitus	12 (36.4%)	7 (46.7%)	3 (17.6%)	14 (28.6%)	-
Hyperlipidemia	9 (27.3%)	7 (46.7%)	3 (17.6%)	29 (59.2%)	-

BP, blood pressure; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate
Normocalcemia, 9.8–10.1 mg/dL; hypercalcemia, 10.2–13.4 mg/dL; low PTH, 8–49 pg/mL; high PTH, 50–440 pg/mL

in both hypercalcemic and normocalcemic groups (Fig. 3). Logistic multiple regression analysis determined that serum calcium and PTH levels were positive contributors to hypertension, respectively (Table 4, Models 1 and 2); however, strong association between levels of serum calcium and serum PTH does not allow to put them into logistic regression analysis simultaneously. We therefore, could not conclude whether PTH and calcium independently contribute to incidence of hypertension.

pPHT is a risk factor for incidence of hypertension

We divided subjects into two groups: patients with clinically definite pHPT with detectable parathyroid lesions or biochemically probable pHPT without detectable parathyroid lesions, and patients except definite or probable pHPT such as healthy subjects and other metabolic disorders (Table 3). In patients with pHPT, 39 patients (57.4%) had parathyroid lesions detected by echography. The prevalence of hypertension was higher in patients with definite and probable pHPT than

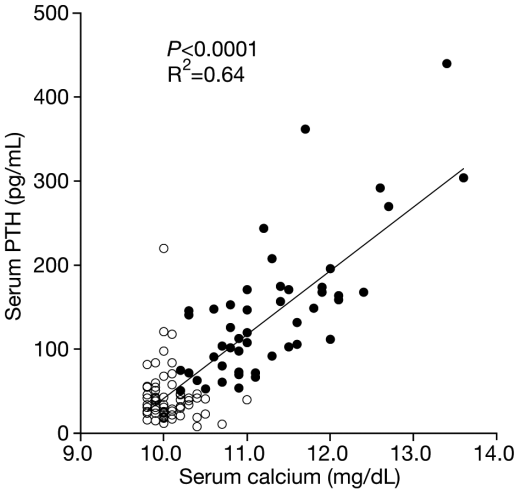

Fig. 1 Association between serum calcium and PTH levels ●, patients with hypercalcemic (10.2–13.4 mg/dL) and high PTH (50–440 pg/mL); ○, patients without hypercalcemic and high PTH

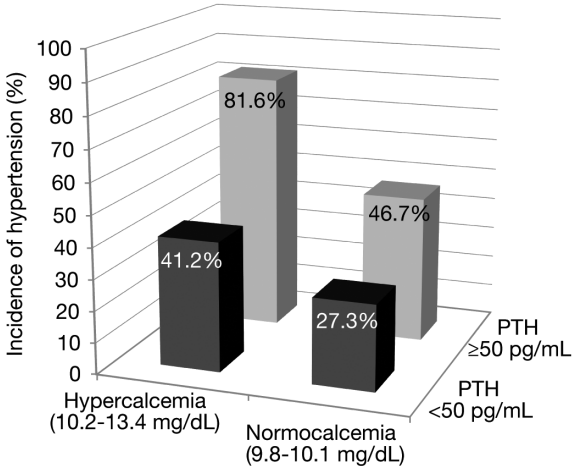

Fig. 3 Associations between serum calcium, PTH levels, and the prevalence of hypertension

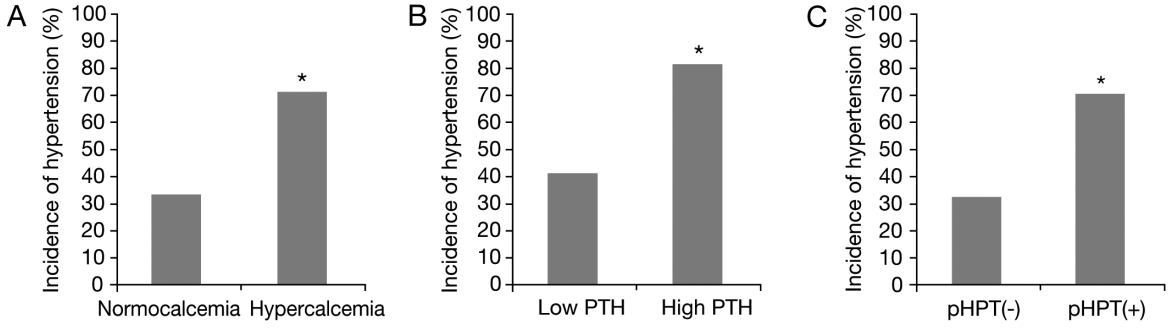

Fig. 2 A: Comparison of the prevalence of hypertension between hypercalcemic and normocalcemic groups (* $P < 0.001$)
B: Comparison of the prevalence of hypertension between high and low PTH groups (* $P < 0.001$)
C: Comparison of the prevalence of hypertension between patients with pHPT and patients without pHPT (* $P < 0.001$)

Table 3 Clinical characteristics of the patients with/without pHPT

Variables	pHPT (−)	pHPT (+)	*P*-value
Number of patients	46 (40.4%)	68 (59.6%)	
Male	23 (50.0%)	13 (19.1%)	<0.001
Age (years)	50.5 ± 14.9	60.8 ± 13.7	<0.001
Body mass index	23.5 ± 5.7	23.5 ± 4.2	0.99
Systolic BP (mmHg)	126.3 ± 14.6	136.7 ± 20.4	<0.01
Diastolic BP (mmHg)	70.1 ± 10.8	77.2 ± 15.0	0.25
Serum calcium (mg/dL)	9.9 ± 0.17	10.9 ± 0.84	<0.001
Serum albumin (g/dL)	4.3 ± 0.4	4.1 ± 0.4	<0.001
Corrected serum calcium (mg/dL)	10.0 ± 0.2	11.0 ± 0.84	<0.001
Serum PTH (pg/mL)	30.2 ± 12.6	123.0 ± 79.2	<0.001
eGFR (mL/min/1.73m^2)	78.4 ± 22.8	70.2 ± 23.1	0.03
Complications			
Diabetes mellitus	16 (48.2%)	20 (29.4%)	0.54
Hyperlipidemia	13 (45.5%)	35 (51.5%)	0.01

BP, blood pressure; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate

Table 4 Determinants of hypertension

Model 1

Variables	OR	95% CI	*P*-value
Age	1.01	1.00–1.02	0.14
Male sex	6.80	1.77–31.2	< 0.01
Body mass index	1.18	1.04–1.36	0.01
Diabetes mellitus	0.68	0.19–2.36	0.55
Hyperlipidemia	6.79	1.77–31.2	0.03
Serum PTH	1.01	1.00–1.02	< 0.01
eGFR	0.97	0.94–0.99	0.01

Model 2

Variables	OR	95% CI	*P*-value
Age	1.03	0.99–1.08	0.19
Male sex	4.70	1.26–20.1	0.03
Body mass index	1.16	1.02–1.33	0.03
Diabetes mellitus	0.91	0.24–3.38	0.89
Hyperlipidemia	3.93	1.10–15.5	0.04
Serum calcium	3.06	1.34–8.37	0.02
eGFR	0.97	0.94–0.99	0.04

Model 3

Variables	OR	95% CI	*P*-value
Age	1.03	0.99–1.08	0.12
Male sex	3.19	1.02–10.9	0.05
Body mass index	1.16	1.02–1.32	0.02
Diabetes mellitus	0.84	0.26–2.63	0.76
Hyperlipidemia	4.44	1.45–14.9	0.01
pHPT	4.82	1.75–14.4	< 0.01
eGFR	0.98	0.95–1.00	0.12

OR, odds ratio; CI, confidence interval; PTH, parathyroid hormone; eGFR, estimated glomerular filtration rate, pHPT; primary hyperparathyroidism

in patients without pHPT (Fig. 2C). Logistic multiple regression analysis determined that the presence of pHPT, BMI, and presence of hyperlipidemia were positive contributors to the prevalence of hypertension; however, age, male sex, eGFR and the presence of diabetes mellitus were statistically excluded (Table 4, Models 3).

The effects of parathyroidectomy on blood pressure

Of the sample, 29 patients with pHPT underwent parathyroidectomy; 4.5 ± 3.1 months after the surgery, systolic blood pressure had significantly decreased from 138.2 ± 14.9 to 128.0 ± 11.0 mmHg ($P < 0.01$), while the decrease in diastolic blood pressure from 77.4 ± 12.2 to 74.8 ± 10.1 mmHg was not significant ($P = 0.29$).

Discussion

In this study, we determined that high serum levels of PTH and calcium are risk factors for hypertension in Japanese patients. Our results suggest that high PTH and calcium synergistically affect the prevalence of hypertension.

PTH levels are associated with all cause and cardiovascular mortality [2, 3]. PTH receptors are expressed in the vessel wall and myocardium and may be involved in the pathological process of cardiovascular disease, leading to vascular stiffness and left ventricular hypertrophy [13]. Therefore, PTH can induce hypertension in both a calcium-dependent and -independent manner, leading to PTH-related cardiovascular disease.

Serum calcium levels are independent predictors of mortality, even in the normal range [14]. Infusion of calcium to healthy volunteers increased blood pressure [15], possibly in a calcium-dependent manner through the calcium-sensing receptor (CASR), which is expressed in the parathyroid, brain, and kidneys. CASR expressed in the thick ascending limb inhibits the Na-K-2Cl cotransporter, resulting in a decrease in sodium reabsorption and a secondary decrease in calcium reabsorption. Therefore, it is suggested that CASR gene variants influence blood pressure by affecting sodium retention [16].

PTH also plays an important role in elevating blood pressure in a calcium-independent manner, as infusion to normal subjects results in hypertension and increased levels of serum calcium. Serum PTH levels are also related to blood pressure, particularly nocturnal blood pressure in the elderly [17]. Intracellular calcium levels are strongly correlated with PTH levels in patients with pHPT. Successful removal of a parathyroid adenoma decreased intracellular calcium and serum PTH levels, suggesting that PTH acts as an ionophore for calcium entry into cells [4, 5, 9]. Vascular contraction is predicted to be induced by increased calcium uptake through the direct and indirect effects of PTH, such as activation of vitamin D. On the other hand, the PTH/PTH -related peptide receptor of vascular smooth muscle cells can increase intracellular cyclic adenosine monophosphate levels, leading to vasodilation [18]. These contradicting results suggest the double-sided effects of PTH.

In addition, impaired endothelium-dependent vasodilation and disturbed endothelial function were reversed in pHPT patients by parathyroidectomy, suggesting that

hypertension in pHPT patients might be attributable to endothelial damage [19]. Other mechanisms of PTH-induced hypertension include activation of the renin-aldosterone system [20], secretion of cortisol from the adrenal cortex [21], and sympathetic activity [22]. High blood pressure is associated with loss of calcium in the urine, leading to a negative calcium balance for bone remodeling [23]. Urinary calcium loss is associated with an increase in the secretion of PTH, which may enhance the incidence of hypertension [24].

Our present study had several limitations. Since we could not evaluate the effects of 1,25-$(OH)_2$ vitamin D and 25-(OH) vitamin D levels on incidence of hypertension due to data deficiency, further examinations about vitamin D-related metabolism is needed to clarify this issue. In addition, we were unable to obtain accurate information regarding the family history of hypertension. Finally, this was a retrospective study with a small sample size in a single center. Large, clinical cohort studies are needed to clarify these issues.

In conclusion, high serum levels of both PTH and calcium are risk factors for hypertension in Japanese patients.

Acknowledgments

We thank the staff of the Hospital Information Center of Tokushima University Hospital for abstracting patients' data from medical records. This work was supported in part by JSPS KAKENHI (Grant Number 25461131).

Disclosure

The authors declare that they have no conflicts of interest to disclose.

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