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Original article

Relationship between parathyroid levels and the size and number of the parathyroid glands in renal hyperparathyroidism

Thanattha Intrarak, Tunchanok Paprad, Netsiri Dumromgpisutikul*

Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Redcross Society, Bangkok, Thailand

Abstract

Background: The gold standard for diagnosing renal hyperparathyroidism (RH) is serum parathyroid hormone (PTH). Parathyroid gland (PTG) hyperplasia is a result of persistent hyperparathyroidism in patients with chronic kidney disease. Consequently, the PTG size could serve as a substitute indicator for determining the degree of hyperparathyroidism.
Objective: Our study aimed to investigate the relationship between serum PTH levels and the size and number of PTGs in patients with RH.
Methods: We retrospectively identified patients from August 1, 2010, to June 30, 2019, with RH who underwent ultrasonography of the PTGs at our institution. The summations of the maximal diameters and number of enlarged PTGs were collected and compared with the serum PTH levels.
Results: We explored 110 PTGs in 40 patients. Serum PTH levels and the summations of the maximal diameters of the PTGs correlated positively ($r = 0.397$, $P < 0.05$). There was statistical significance in the prediction of parathyroid enlargement (≥3 glands) (AUC = 0.659, 95% CI: 0.482–0.836, $P = 0.085$). High specificity (>81.0%) was obtained for detecting ≥3 parathyroid gland enlargements at a cut-off PTH level of >2,100 pg/ml.
Conclusion: There was a positive correlation between the size of the PTG and the serum PTH levels in RH patients. Individuals with higher PTH levels also had more number of PTGs. The discrepancy between the PTG size and the serum PTH level may indicate further exploration for additional PTGs.

Keywords: parathyroid hormone, Renal hyperparathyroidism, ultrasound.

Chronic kidney disease (CKD) is a major global health issue. Renal hyperparathyroidism (RH) is a frequent complication in CKD stages 3–4, characterized by an elevation of parathyroid hormone (PTH) levels secondary to an imbalance of Ca, phosphate, and vitamin D homeostasis. [1] RH is classified into two types based on the patient's serum Ca levels. Secondary hyperparathyroidism (SHPT) involves the overproduction of PTH in response to hypocalcemia. Tertiary hyperparathyroidism occurs when long-standing SHPT develops autonomous PTH secretion, even though the Ca level is high.

***Correspondence to: Netsiri Dumromgpisutikul,** Department of Radiology, Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial Hospital, Thai Redcross Society, Bangkok 10330, Thailand
E-mail: netsiri.d@chulahospital.org
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The gold standard for diagnosing RH is the serum PTH level. Parathyroid gland (PTG) hyperplasia develops as a result of persistent hyperparathyroidism in patients with CKD. Consequently, the PTG size could serve as a substitute indicator for determining the degree of hyperparathyroidism. [2] Moreover, a supportive study revealed a positive correlation between the size and weight of the excised PTGs in individuals with >1,000 pg/ml PTH levels. [4]

SHPT can be treated with calcimimetic drugs. However, many do not respond to these and require operative treatment.[1] Minimally invasive parathyroidectomy (MIP) is a safe, efficient surgical procedure for the treatment of hyperparathyroidism, with smaller surgical incisions, shorter operating durations, and quicker recovery periods.[5, 6] PTGs can be imaged using ultrasound, and nuclear medicine-based noninvasive techniques such as single photon emission computed tomography/computed tomography (SPECT/CT), computed tomography

(CT), and magnetic resonance imaging.[2] These can be applied for precise preoperative localization, which is essential for planning MIP.[6 - 8] High-resolution ultrasonography, a cost-effective method, is readily accessible for identifying enlarged PTGs, demonstrating sensitivity, specificity, and positive predictive values at 62.5%, 85.7%, and 87.5%, respectively.[3] Ultrasonography is easily performed and does not cause radiation harm. The size of parathyroid lesions can be measured simply. However, ultrasonography has the drawbacks of being dependent on the operators, machines, and patients. Some limitations of measurement may occur due to the location of the PTGs.

This study primarily aimed to demonstrate the relationship between serum PTH levels and the size and number of enlarged PTGs in RH. Our secondary objective was to evaluate the relationship between the calcified aortic arch and PTH level.

Materials and methods

Study population

We retrospectively analyzed patients who underwent ultrasonography of the PTGs at our institution from August 1, 2010, to June 30, 2019. The inclusion criteria were as follows: 1) CKD patients; 2) 18–80 years old; 3) diagnosed with RH; 4) had a high PTH level (>65 pg/ml); and 5) had parathyroid hyperplasia identified by ultrasound. For all patients, PTH levels were obtained within 3 months before or after PTG ultrasonography. The exclusion criteria were previous parathyroidectomy, those with known ectopic or residual PTGs, postrenal transplant patients, and pregnant women.

Study design

This retrospective study was approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University. The ultrasonographs of the PTGs, stored in our hospital's picture archiving and communication system, were independently reviewed by two researchers blinded to patient information and laboratory data. Our hospital's standard protocol for parathyroid ultrasound employs linear high-frequency transducers ML 6-15 (bandwidth 4–15 MHz) to examine the central and lateral compartments of the neck, including areas around the thyroid gland, above and below it, and the neck node.

In our study, many PTGs were found located inferiorly, which hindered three-dimensional (3-D) measurement. We chose to use the summations of the maximal diameters of each enlarged PTG as a representation of the gland size in each patient. This approach provides greater practicality for routine clinical use. Based on the ultrasound, PTG hyperplasia appears as a well-defined oval, bean, or multilobulate-shaped hypoechoic lesion located along the posterior or inferior aspect of the thyroid gland. [9]

The calcified aortic arch was graded in a separate session from the PTG imaging, which was blinded to the laboratory and PTG imaging data. The grading was on a 4-point scale employing a modified method reported previously, which incorporated the proportion of circumferential calcification as illustrated in **Figure 1**. Grade 0 indicated no visible calcification; grade 1 indicated <50.0% calcification; grade 2 indicated >50.0% calcification; and grade 3 indicated circumferential calcification.[10, 11] Disagreements regarding imaging results and grading scores were resolved through consensus.

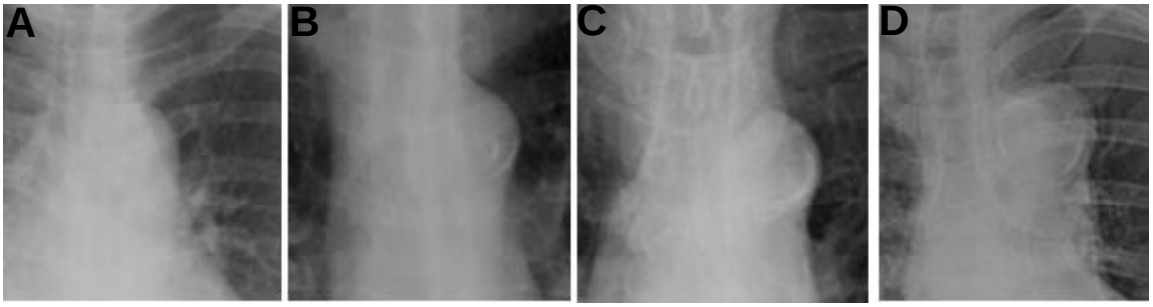

Figure 1. Grading score of aortic arch calcification from chest radiographs**(A)** Grade 0; **(B)** Grade 1; **(C)** Grade 2; **(D)** Grade 3.

Statistical analysis

Statistical analyses used STATA/IC 14.0 (Stata Crop., TX, USA) to detect significant differences. The relationships between the summations of maximal diameters, the number of enlarged PTGs, and serum PTH levels were investigated using Pearson's correlations, Analysis of variance, and unpaired Student's *t*-tests. The correlations between serum Ca level and the calcified aortic arch grading score were investigated using Spearman correlations. Statistical significance was defined as a $P < 0.05$.

Results

Clinical parameters of RH patients undergoing parathyroid gland imaging

This study included 40 patients. **Table 1** summarizes their baseline characteristics and clinical data. Most (87.5%) had multiple gland enlargement, with only five having single gland enlargement.

The time interval between the ultrasound scan of the PTGs and the serum PTH measurement ranged from 0 to 66 days. They were performed on the same day in 57.5% of the patients, while 30.0% underwent the blood test within one month of the ultrasound.

A total of 110 enlarged PTGs were included. The ultrasonographic features of all enlarged glands are shown in **Table 2.** Most of them appeared as well-defined, oval-shaped hypoechoic lesions. Heterogeneous echo was frequently observed. Examples of these features are shown in **Figure 2.** The enlarged PTGs were mostly located inferior to the thyroid gland, with 38 and 34 glands in the right inferior and left inferior locations, respectively. Other locations included five glands located posterior or medial to the right mid-thyroid gland and two located posterior to the left mid-thyroid gland.

The calcified aortic arch was graded in 17 patients; five each (29.4%) and two (11.8%) were classified as grades 0, 1, 2, and 3, respectively.

The biochemical profiles of the patients are shown in **Table 3**. The mean serum PTH levels were 1688.5 pg/ml (125.4–4677.0), and the mean serum Ca levels were 10.2 mg/dl (8.1–12.0).

Serum PTH levels and summations of the maximal diameters of the parathyroid glands.

As shown in **Figure 3**, the summations of the maximal diameters of the enlarged PTGs positively correlated with the serum PTH levels ($r = 0.397$, $P = 0.01$). After classifying the PTH levels into four groups (<1000, 1000–1999, ≥2000–2999, and ≥3000 pg/ml), there were statistically significant larger summations of maximal diameters when comparing PTH levels <1000 pg/ml and 2000–3000 pg/ml **(Table 4)**. Comparing patients with PTH levels <1000 *vs*. ≥1000 pg/ml, there were markedly greater summations of the maximal diameters of the enlarged PTGs in the higher PTH level group **(Table 5).** There was also a statistical significance in predicting parathyroid enlargement of ≥3 glands ($P = 0.085$, AUC: 0.659, 95% CI: 0.482–0.836) as shown in **Figure 4**. High specificity (>81.0%) was achieved when using a cut-off PTH value of >2100 pg/ml.

Correlation of serum Ca levels with the calcified aortic arch grading score

In 17 patients who underwent chest radiographs within 12 months before or after ascertaining serum Ca, both were not significantly correlated ($r = 0.356$, $P = 0.153$).

Table 1. Baseline characteristics of the patients (n = 40)

Male (%)	17 (42.5%)
Age (year), mean ± SD	47.5 ± 11.4
Underlying disease (%)	
Diabetes mellitus	10 (25.0%)
Hypertension	27 (67.5%)
Others	20 (50.0%)
Number of parathyroid glands enlargement (%)	
1	5 (12.5%)
2	16 (40.0%)
3	6 (15.0%)
4	9 (22.5%)
5	4 (10.0%)

Table 2. Ultrasonographic features of parathyroid hyperplasia.

Total number of parathyroid hyperplasia (n = 110)	
Location	
Right superior	16
Right inferior	38
Left superior	15
Left inferior	34
Others	7
Calcific features	
Peripheral calcification	17
Internal calcification	1

Figure 2. Ultrasonographic features of enlarged parathyroid glands. **(A)** Peripheral calcification; **(B)** Internal calcification; and **(C)** Heterogeneous echo.

Table 3. Baseline laboratory parameters in the study subjects.

Parameters	**N**	**Mean**	**SD**	**Median**	**Lower limit**	**Upper limit**
PTH (pg/ml)	40	1687.6	961.5	1688.5	125.4	4677.0
< 1,000				10 (25.0%)		
1,000 - 1,999				14 (35.0%)		
2,000 - 2,999				14 (35.0%)		
> 3,000				2 (5.0%)		
ALP (U/L)	25	392	468	251	69	2322
Serum albumin (g/dl)	40	4.2	0.5	4.3	3.2	5.4
Serum calcium (mg/dl)	39	10.1	1.0	10.2	8.1	12.0
Serum phosphorus (mg/dl)	39	5.1	2.1	5.3	2	9.5

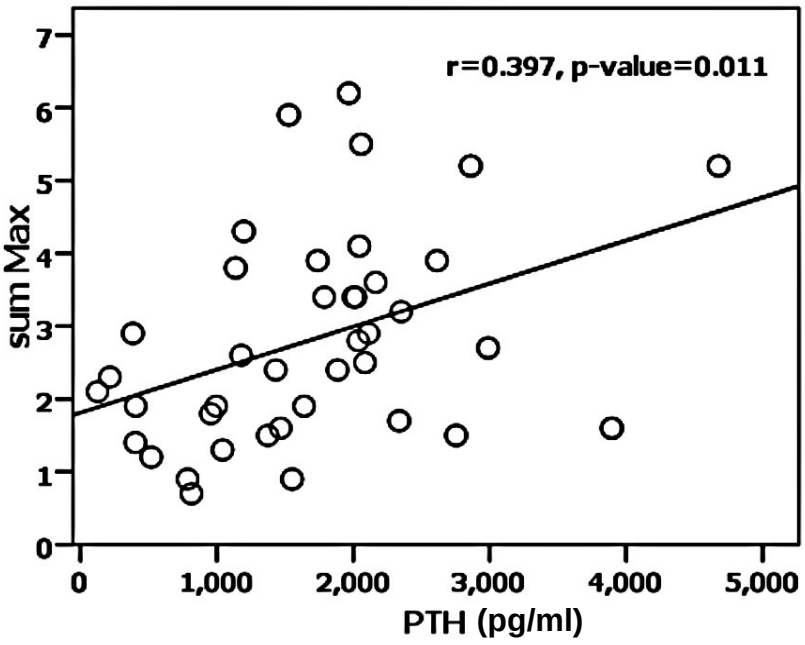

Figure 3. Scatter plot of summations of maximal diameters (sum max) of parathyroid glands and PTH level.

Table 4. PTH level with summations of maximal diameters and summations of numbers of parathyroid glands.

PTH (pg/ml)	Summations of maximal diameters				Summations of numbers		
	N	Mean ± SD	Median (min, max)	*P*-value	Mean ± SD	Median (min, max)	*P*-value
< 1,000	10	1.7 ± 0.7*	1.9 (0.7, 2.9)		2.0 ± 0.7	2.0 (1, 3)	0.116
1,000 - 1,999	14	3.0 ± 1.7	2.5 (0.9, 6.2)	0.034*	2.8 ± 1.2	3.0 (1, 5)	
2,000 - 2,999	14	3.3 ± 1.1*	3.3 (1.5, 5.5)		3.3 ± 1.6	4.0 (1, 6)	
≥ 3,000	2	3.4 ± 2.6	3.4 (1.6, 5.2)		2.5 ± 0.7	2.5 (2, 3)	

P-value by ANOVA test.

Table 5. Unpaired student's *t* - test of PTH level with summations of maximal diameters and summations of numbers of parathyroid glands.

PTH (pg/ml)	N	Summations of maximal diameters	*P*-value	Summations of numbers	*P*-value
< 1,000	10	1.7 ± 0.7	< 0.001*	2.0 ± 0.7	0.004*
≥ 1,000	30	3.2 ± 1.4		3.0 ± 1.4	
< 1,500	17	2.0 ± 1.0	0.002*	2.1 ± 0.8	0.003*
≥ 1,500	23	3.4 ± 1.5		3.2 ± 1.4	
< 2,000	24	2.5 ± 1.5	0.062	2.5 ± 1.1	0.107
≥ 2,000	16	3.3 ± 1.3		3.2 ± 1.5	

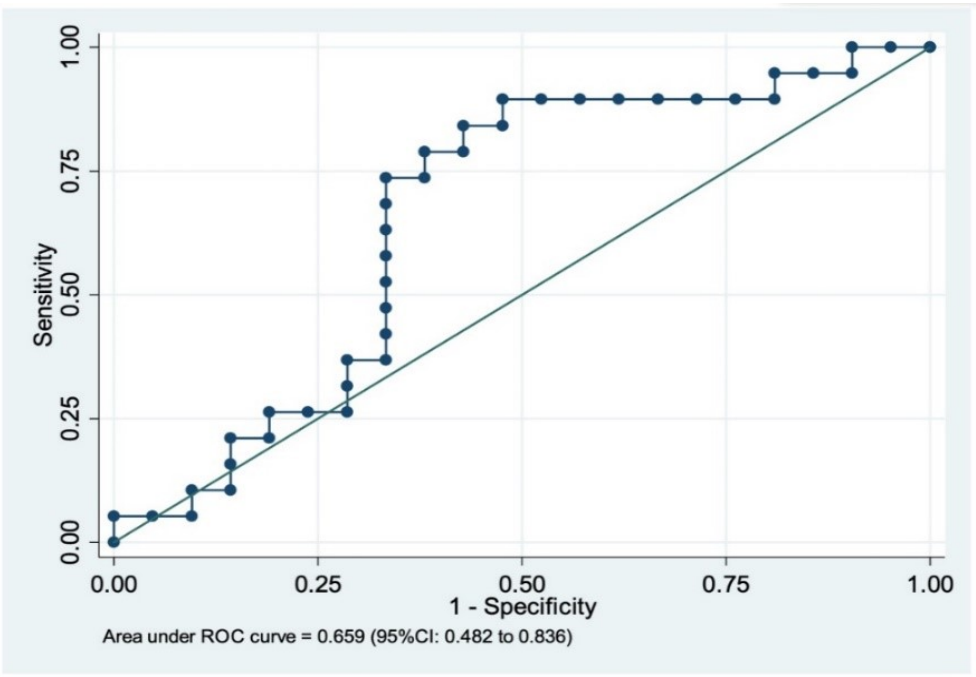

Figure 4. Receiver operating characteristic. The area under the curve (AUC 0.650, 95% CI 0.482 - 0.836) measures the ability of PTH level to predict enlarged parathyroid glands ≥ 3 glands.

Discussion

SHPT occurs owing to CKD, in which vitamin D is not converted into the physiologically active 1,25-cholecalciferol. This condition lowers the intestinal absorption of Ca, resulting in hypocalcemia and failure to excrete phosphate, leading to hyperphosphatemia. These in turn increase the stimulation of the PTGs, causing their hyperplasia and enhanced PTH secretion. [12] Based on this pathophysiology, we hypothesized that PTH levels should be linearly correlated with PTG size.

Our theory is supported by an earlier work, which demonstrated a positive association between the size and weight of the surgically removed PTGs in 223 patients and the preoperative PTH levels in those with PTH levels >1000.[4] However, the relationship between the PTG size measured by ultrasound and PTH levels in prior studies is still controversial. Positive correlations were detected between the ultrasonography-based size and calculated volume and the actual weight and total mass of the surgically excised gland, as well as between the mass of individual glands and the PTH levels 15 min after removal.[13]

A marked correlation has been reported between the ultrasonographic size of the PTGs and the PTH levels in SHPT patients. [14] However, in another study the volume of PTGs calculated from 3-D ultrasonographic diameters did not correlate remarkably with serum PTH. [15] Similarly, no significant correlation between gland size measured by ultrasound and PTH levels was detected, although some trends toward statistical significance were observed, suggesting further explorations in larger studies.[16] These discrepant results could be explained by the limitations of ultrasonography, including variability in technique, operator skill, and patient-related factors. Ultrasonography of the PTGs is anatomically challenging due to their difficult locations. While most are located at the posterior or inferior aspect of the thyroid gland, ectopic glands occur in areas such as the retropharyngeal or retroesophageal regions for the superior PTGs and from the mandibular angle to the pericardium for the inferior PTGs. [17, 18] Uslu et *al.* reported ectopic glands more frequently in the inferior positions[18], while Fang et *al.* found no apparent preference.[19] In our study, enlarged glands were often in the inferior position (right inferior = 34.5%, left inferior = 30.9%), complicating 3-D measurements. To examine more practical parameters, our study explored the relationship using summations of the maximal diameters, avoiding the need for 3-D measurements and complex calculations.

Our study found a marked correlation between the summations of the maximal diameters of the enlarged PTHs and serum PTH levels, as well as significant differences when comparing the lower and higher PTH level groups. The cut-off value for predicting >1 enlarged PTG did not yield a high area under the ROC curve, which could be explained by most patients having high PTH levels (>1,500 pg/ml = 57.5%) and multiple enlarged PTGs (87.5%). On the other hand, high specificity (>81.0%) was obtained for detecting ≥3 PTG enlargements at a cut-off PTH level of >2,100 pg/ml, which aligned with the outcome of the independent *t*-test. This result can serve as a guide during surgical planning, indicating the need to explore the neck <3 enlarged glands are found. Roughly, the summations of maximal diameters were 2 cm with an average of two enlarged PTGs in PTH levels <1,000 pg/ml, and 3 cm with an average of three enlarged PTGs in levels ≥1,000 pg/ml. These findings help improve the confidence of radiologists and radiographers while examining parathyroid ultrasonography results and the accuracy of enlarged PTG detection.

Aortic arch calcification can be reliably identified using chest radiography, a simple and widely accessible method. [11] It is a significant predictor of cardiovascular outcomes, including coronary heart disease andischemic stroke. [20,21] However, our study identified no marked correlation between serum Ca levels and calcified aortic arch score grading. This observation may be due to uncontrolled factors such as age, smoking, hypertension, and dyslipidemia.[21]

Our study did have some limitations. First, it was retrospective with a relatively small sample size. Larger, prospective studies designed to control interfering factors and variability between patients, such as medications and time intervals between blood tests and ultrasonographic studies, may help validate our findings. However, our study intended to assist actual clinical practice in sonographers, radiologists, and physicians. Second, the operator-dependent nature of ultrasonography may affect measurement precision and reproducibility. The use of the summation of maximal diameters as a measure of PTG enlargement in our study helps reduce variability, is less time-consuming, and avoids the complex calculations required for 3-D measurements. Finally, the pathological confirmation of parathyroid hyperplasia was unavailable for most patients included in our study because parathyroidectomy or tissue biopsies were not performed. Further studies with selective inclusion of only surgically indicated patients are suggested.

Conclusions

The size of the PTG and the serum PTH levels were positively correlated in patients with RH. Individuals with elevated PTH levels also had more number of PTGs. The discrepancy between the PTG size and the serum PTH levels may indicate further exploration for additional PTGs.

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Conflicts of interest statement

All authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors disclose any conflicts of interest.

Data sharing statement

All data generated or analyzed during the present study are included in this published article. Further details are available for noncommercial purposes from the corresponding author upon reasonable request.

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