The relationship between parathyroid enlargement and parathyroid hormone levels in patients undergoing hemodialysis; EMR(Electronic Medical Record)

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Abstract

Background/Objectives: The diagnostic role of parathyroid gland ultrasonography in secondary hyperparathyroidism
is controversial. We used ultrasonography to investigate parathyroid gland enlargement in patients undergoing hemodialysis at a single center.

**Methods/Statistical analysis:** High-resolution thyroid and parathyroid ultrasonography was performed in 86 patients undergoing maintenance hemodialysis. Laboratory data in electronic health record (EHR) systems included blood hemoglobin, albumin, phosphorus, calcium, alkaline phosphatase, Ca × P product, and iPTH. We evaluated age, sex, and underlying renal diseases. Variables such as etiology, hemodialysis duration, and usage of hyperparathyroidism-related medications were analyzed to assess their correlation with high-resolution ultrasonography detection of parathyroid enlargement.

**Findings:** We categorized patients according to the presence (detected group; N = 28) or absence (undetected group; N = 58) of enlarged parathyroid glands. Enlarged parathyroid glands were detected in 28 patients (33%), with single-gland enlargement in 21 (25%) and enlargement of ≥2 glands in 7 (8%). iPTH levels were significantly different between patients with and without parathyroid enlargement (p<0.05). Among the 28 patients with parathyroid enlargement, 16 (57%) had acceptable iPTH levels (<300 pg/mL) and 12 (43%) had high iPTH levels (>300 pg/mL).

**Improvements/Applications:** This cross-sectional study is intended to investigate PTG enlargement and to perform biochemical examinations in patients undergoing hemodialysis at a single center.

**Key Words:** Parathyroid enlargement, Secondary hyperparathyroidism, Parathyroid hormone, Hemodialysis, Ultrasonography, EMR (Electronic Medical Record).

1 **Introduction**

It is Secondary hyperparathyroidism (SHP) that CKD patients can suffer as one of the important complications. SHP is associated with bone complications and an increase in cardiovascular mortality. The diagnostic role of ultrasonography (US) of the parathyroid glands (PTG) in uremic secondary hyperparathyroidism (SHPT) is
still controversial. Clinically, US is the most reliable technique for accurate measurement of the size and location of the PTG and is a useful noninvasive method for evaluating SHPT. The sensitivity and specificity of US for the detection of primary parathyroid adenoma (8095%) is higher than that for secondary hyperplasia involving all PTG (6075%). However, most clinicians continue to use US as an indispensable tool for identification of the PTG prior to surgery. Many studies report that US is very sensitive for detecting PTG enlargement and that US results correlate well with histopathological findings of surgically resected specimens. Takebayashi et al and Restrepo Valencia et al reported that, independently of the intact parathyroid hormone (iPTH) level, they used US to detect hyperplasia in an average of 2.3 glands per patient in 30% out of 207 patients on dialysis.

PTH is formed in the PTG and secreted into the bloodstream; iPTH is a polypeptide containing 84 amino acids, and has a molecular weight of approximately 9. The half-life of active N-terminal fragment takes only a few minutes. PTH, together with vitamin D and calcitonin, mobilizes calcium and phosphate from the skeletal system and increases intestinal calcium uptake and renal phosphate excretion. Blood calcium is maintained at a constant level by the interaction of PTH and calcitonin. Hyper functioning of the PTG results in an increased secretion of PTH (hyperparathyroidism). Primary causes are adenomas of the PTG. In SHPT, the blood calcium level is low because of other pathological states such as vitamin D deficiency. Hyperparathyroidism secondary to hemodialysis is a serious complication, as it is associated with osteodystrophy, vascular calcifications, and high cardiovascular morbidity and mortality. SHPT is a complication of CRF caused by various etiologies and compensatory hypersecretion of PTH. PTH levels in patients undergoing hemodialysis increase because of low concentrations of 1,25 (OH)₂ D₃, phosphorous retention, and a reduction in serum calcium and the expression of calcium-sensitive vitamin D receptors. Importantly, cells that constitute the hyperplasic PTG experience a reduction in the number of receptors for vitamin D and calcium, and this reduction is greater in nodules.

Typically, serum PTH concentrations have been used to establish the degree of hyperparathyroidism in CKD patients. However, the use of US to detect changes in PTG size has recently increased...
because of its therapeutic and prognostic implications. In CKD pa-
tients, PTG initially grow in a diffuse and polyclonal way and then
progress to nodular hyperplasia. If this nodular growth is not ade-
quately treated, it can result in autonomous monoclonal cell pro-
iferation and a high potential of aggressive growth. The factors
connected with this pattern of progression as well as any under-
lying genetic mutations remain unclear. Thus, the metabolic
changes that occur in CKD could be an important factor in trig-
gerating these events. The cells that form the PTG with nodular
hyperplasia are affected by a decrease in the number of vitamin D
and calcium receptors. This deduction makes the receptors re-
fractory to conventional medical therapy. We can detect PTG with
nodular hyperplasia in CKD patients through high-resolution US.
Offering the best therapeutic option for patients. This inexpensive
and noninvasive radiological study does not have adverse effects.
Also it can be repeated whenever it is needed without exposure to
ionizing radiation confirming correlation between the presence of
PTG larger than 300 mm^3 through US and clinical and laboratory
changes in CKD patients would help figure out populations who
require routine US study. Although a few studies have tried to
confirm this correlation, their results are limited and controversial.

In a previous study conducted in 17 hemodialysis centers through-
out Korea, serum calcium, phosphorus, and iPTH levels were mea-
sured in 1,018 patients. The mean serum levels of phosphorus,
calcium and the Ca × P product were 5.3 mg/dL, 9.1 mg/dL, and
48.0 mg^2/dL^2, respectively. When classified by the recommended
range according to the KDOQI guidelines, about half the patients
had uncontrolled hyperphosphatemia > 5.5 mg/dL. In addition, 270
patients (26.5%) had iPTH levels > 300 pg/mL, whereas 435 pa-
tients (42.7%) had iPTH levels < 150 pg/mL. This study revealed
the current status of CKD-mineral bone disorder (CKD-MBD) in
patients undergoing hemodialysis, indicating that a relatively mod-
erate proportion of patients had assorted outside the target range.

Therefore, in this study, we first determined the prevalence of
PTG enlargement, assessed by US, in patients undergoing mainte-
nance hemodialysis at a single center. We then evaluated the corre-
lation between iPTH levels and US examination results. Moreover,
to enable early intervention in order to decrease complications of SHP such as CKD-MBD, we determined the optimal iPTH cutoff for performance of PTG US.

2 Materials and Methods

From among all patients undergoing maintenance hemodialysis between June 2013 and June 2016 at the Dialysis Unit of the Department of Medicine of the MI JUNG KANG Internal Medicine Clinic, 86 were included in this study. Before subjects enrollment of the experiment, we fully explained its importance and got written consents. A skilled specialist evaluated PTG vascularity and 3-dimensional size. The volume of each PTG was calculated as follows: PTG volume = \((a \times b \times c) \times \pi / 6\). The minimum detectable size of the PTG was approximately 7 mm\(^3\) [figure 1]. US of the PTG was performed using an RS80A with a L3-12A linear array probe (Samsung Medison Co. Ltd., Seoul, Korea). US examination of the anterior neck was performed from the submandibular to subclavicular regions, with the patient in the supine position and the neck extended. PTG were recognized as homogeneously echogenic oval structures, with less echogenicity than the thyroid gland. Laboratory data included blood hemoglobin, albumin, phosphorus, calcium, alkaline phosphatase, \(Ca \times P\) product, and iPTH levels. Patient iPTH concentrations were determined using a chemiluminescent immunoassay and phosphorus, and \(Ca\) and ALP concentrations were determined using spectrophotometry. We also evaluated age, sex, and underlying renal diseases. Different such as etiology, duration of the hemodialysis therapy, and usage of medications related to hyperparathyroidism were analyzed in order to determine any significant correlations between these different and the detection of PTG enlargement by high-resolution US.
2.1 Statistical analysis
SPSS (Version 21, SPSS Inc., Chicago, IL, USA) was used for the data analysis, and the results are presented as mean ± standard deviation. To investigate the differences in clinical characteristics, we used Student’s t-test, chi-square test, and one-way ANOVA. Tukey’s post-hoc test was used to test normality. Multiple regression analysis was performed for each variable that showed a correlation. The independent variables of PTG enlargement and their relationships were analyzed using Pearson correlation coefficients. To determine the cutoff value for the presence or absence of PTG enlargement, receiver operating characteristic (ROC) curve analysis was performed, and sensitivity and specificity were calculated. In addition, odds ratios (ORs) were calculated using logistic regression. Medical Window (Version 15.8, MedCalc Inc., Ostend, Belgium) was used in the data analysis. All differences were determined to be statistically significant when p values were less than 0.05.

3 Results and Discussion

Clinical and medication characteristics
The clinical and medication characteristics of patients with detected or undetected PTG enlargement at hemodialysis are shown in [Table 1]. Patients included 62 men and 24 women, with ages ranging from 36 to 86 years (average ± standard deviation, 58.2 ±
11 years). They had undergone maintenance hemodialysis therapy for an average of 110 ± 92 months. US revealed PTG enlargement in 28 of the 86 patients tested (33%). PTG enlargement was identified in a single gland in 21 patients (25%) and in more than two glands in 7 patients (8%).

Table 1. Clinical and medication characteristics of patients with detected or undetected parathyroid enlargement at hemodialysis.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>PTG enlargement detected</th>
<th>PTG enlargement not detected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients (%)</td>
<td>86 (100)</td>
<td>28 (33)</td>
</tr>
<tr>
<td></td>
<td>Age (years)</td>
<td>58.2 ± 11</td>
<td>51.8 ± 8.1</td>
</tr>
<tr>
<td></td>
<td>Male/Female</td>
<td>52/34</td>
<td>20/8</td>
</tr>
<tr>
<td></td>
<td>Duration of hemodialysis (months)</td>
<td>119 ± 52.4</td>
<td>139 ± 105.3</td>
</tr>
<tr>
<td></td>
<td>Diabetes (%)</td>
<td>28 (33)</td>
<td>9 (32)</td>
</tr>
<tr>
<td></td>
<td>Hypertension (%)</td>
<td>70 (81)</td>
<td>25 (89)</td>
</tr>
</tbody>
</table>

| Medication (%) | Calcium carbonate | 11 (13) | 3 (11) | 2 (9) | 1 (14) | 8 (14) |
|                | Acid   | 21 (24) | 10 (36) | 8 (36) | 2 (29) | 11 (19) |
|                | Vitamin D | 5 (7) | 5 (10) | 4 (18) | 1 (14) | 1 (2) |
|                | Calcitriol | 13 (15) | 3 (9) | 2 (9) | 1 (14) | 10 (17) |
|                | Paricalcitol | 4 (5) | 3 (9) | 2 (9) | 1 (14) | 1 (2) |

Continuous variables are presented as mean ± standard deviation; N, intravenous; PTG, parathyroid gland.

PTG enlargement and patient biochemical characteristics
As shown in [Table 2], hemoglobin, phosphorus, calcium, iPTH levels, alkaline phosphatase, and Ca × P product were significantly higher in the patient group in which PTG enlargement was detected (detected group) than in the patients in whom PTG enlargement was not detected (undetected group).
Relationship between PTG enlargement and iPTH levels

Maximum longitudinal diameter and total volume of enlargement were 9.2 ± 3.8 mm and 320 ± 208 mm³, respectively, in patients with a single enlarged PTG, and 12.8 ± 10.8 mm and 1130 ± 541 mm³, respectively, in those with multiple enlarged PTG. The serum iPTH level was 316.6 ± 246.3 pg/mL in patients with a single enlarged PTG, 383.9 ± 332.7 pg/mL in patients with multiple enlarged PTG, and 89.6 ± 86.9 pg/mL in the undetected group. The average serum iPTH level in the detected group was significantly higher than that in the undetected group (p=0.0000) [Table 2].

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommended that iPTH should be controlled at 150-300 pg/mL. In this study, the PTG was enlarged in 16/28 (57.1%) patients when the iPTH level was >300 pg/mL, and in 11/28 (39.2%) patients when the iPTH level was 300-500 pg/mL. Furthermore, even when the iPTH level was below 150 pg/mL, 5/28 (17.8%) patients showed PTG enlargement on US: 4 patients showed single PTG enlargement, and 1 patient showed enlargement of two or more PTG [Figure 2].

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>All patients</th>
<th>PTG enlargement detected</th>
<th>PTG enlargement not detected</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.5 ± 0.8</td>
<td>10.9 ± 1.1</td>
<td>10.3 ± 0.7</td>
<td>0.037*</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.2 ± 0.3</td>
<td>4.2 ± 0.7</td>
<td>4.2 ± 0.3</td>
<td>0.596</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.7 ± 1.3</td>
<td>5.4 ± 1.6</td>
<td>4.5 ± 0.9</td>
<td>0.017**</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.9 ± 0.6</td>
<td>10.04 ± 0.5</td>
<td>9.5 ± 0.8</td>
<td>0.0000**</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>173.5 ± 218.1</td>
<td>383.9 ± 332.7</td>
<td>89.6 ± 86.9</td>
<td>0.0000**</td>
</tr>
<tr>
<td>ALP (IUL)</td>
<td>288.5 ± 497.2</td>
<td>681 ± 890.6</td>
<td>180.9 ± 59.3</td>
<td>0.0000**</td>
</tr>
<tr>
<td>Ca × P product (mg²/dL²)</td>
<td>45.1 ± 1.05</td>
<td>53.2 ± 1.15</td>
<td>42.7 ± 0.85</td>
<td>0.019**</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. ALP, alkaline phosphatase; PTH, intact parathyroid hormone. Ca × P product, calcium phosphorus product. *p<0.05, **p<0.01 vs. undetected
The presence of PTG enlargement and ROC curve analysis

The correlation between the presence or absence of PTG enlargement and different variables was tested, and the results showed that the area under the curve (AUC) values of hemoglobin, phosphorus, calcium, iPTH, alkaline phosphatase, and $\text{Ca} \times P$ product were statistically significant [Table 3]. The highest AUC was found for iPTH, indicating the greatest influence. An ROC curve analysis was performed to find the effective cutoff iPTH value that could indicate PTG enlargement. AUC was used as an index of accuracy.
AUC, sensitivity, and specificity values are shown in Table 3. The largest sum of sensitivity and specificity was determined to be the cutoff value, with 82.1% for sensitivity, 89.1% for specificity, and 191.3 pg/mL for the optimal value [Figure 3]. Fig. 3 shows the ROC curve of iPTH.

Table 3. Receiver operating characteristic curve analysis for determining parathyroid gland enlargement

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0.719</td>
<td>82.14</td>
<td>58.62</td>
<td>0.001*</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>0.495</td>
<td>85.71</td>
<td>26.31</td>
<td>0.938</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>0.679</td>
<td>46.43</td>
<td>84.48</td>
<td>0.007*</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>0.746</td>
<td>92.86</td>
<td>62.34</td>
<td>0.000***</td>
</tr>
<tr>
<td>iPTH (pg/mL)</td>
<td>0.908</td>
<td>82.13</td>
<td>86.71</td>
<td>0.000**</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>0.631</td>
<td>32.14</td>
<td>94.83</td>
<td>0.050</td>
</tr>
<tr>
<td>Ca × P product (mg/dL)</td>
<td>0.713</td>
<td>42.86</td>
<td>93.10</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

ALP, alkaline phosphatase; AUC, area under the curve; Ca × P product, calcium-phosphorus product. *p<0.05, **p<0.01.

Figure 3: ROC curve analysis of parathyroid enlargement by iPTH

*Multiple logistic regression of PTG enlargement*

In the ROC curve analysis, iPTH was determined to be a better predictive factor for PTG enlargement than the other variables.
tested (p = 0.000), with a cutoff value of 191.3 pg/mL (82.1% for sensitivity and 89.1 for specificity). Using multiple logistic regression, we calculated the odds ratio to be 39.86 [Table 4].

Table 4. Distribution of patients with parathyroid enlargement according to iPTH levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>PTG enlargement detected (N = 28)</th>
<th>PTG enlargement not detected (N = 58)</th>
<th>Odds ratio: 39.86</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH &lt; 191.3 pg/mL</td>
<td>6 (21.4%)</td>
<td>52 (91.2%)</td>
<td>9.9 CI p = 0.000</td>
</tr>
<tr>
<td>iPTH ≥ 191.3 pg/mL</td>
<td>23 (82.1%)</td>
<td>6 (20.7%)</td>
<td>11.03 to 144.94</td>
</tr>
</tbody>
</table>

In our study, the PTG enlargement detection rates were similar to those of previous studies, with enlarged PTG appearing as hypoechoic or anechoic masses in 28 out of 86 patients (33%). PTG enlargement was detected in a single gland in 25% of these patients and in two or more glands in 8%. In addition, hemoglobin, phosphorus, calcium, iPTH, alkaline phosphatase, and Ca × P product were significantly higher in the group of patients with enlarged PTG. However, a significant correlation was not detected between PTG enlargement and dialysis duration, age, diabetes, hypertension, or carotid plaques, presumably because of the small number of participants. Additional studies with more patients are needed to confirm these findings.

In Korea, the KDOQI and Kidney Disease guidelines are well known and commonly used to improve the quality of care in CKD-MBD. In addition, global and regional guidelines as well as suggested target ranges and treatment protocols have been established for CKD-MBD, which is a common complication in CKD patients, in addition to hypercalcemia and hyperphosphatemia, CKD-MBD can cause vascular calcification and cardiovascular diseases (CVD), and these conditions are closely associated with an increased mortality rate. Recently, these associations have been demonstrated, even in early-stage CKD patients. The mean serum levels of phosphorus, calcium, and the Ca × P products of patients in the present study indicate that their conditions were relatively well managed in comparison with the patients in a study by Ganesh et al., in which the mean serum levels of phosphorus, calcium, and the Ca × P product were 6.2 ± 2.0 mg/dL, 9.4 ± 1.0 mg/dL, and 57 mg²/dL², respectively.
The KDOQI guidelines recommend that iPTH levels should be between 150 and 300 pg/mL. In this study, however, when the iPTH level was below 150 pg/mL, 14.3% patients showed a single enlarged PTG and 3.6% showed two or more enlarged PTG. Furthermore, when the iPTH level was below 300 pg/mL, enlarged PTG were observed in 57% of all patients with enlarged PTG. Thus, we were able to detect PTG enlargement early by using PTG US even when the iPTH level was below 300 pg/mL, which is within the normal range. We conducted a retrospective analysis to identify independent factors that caused PTG enlargement and found that iPTH, hemoglobin, \( \text{Ca} \times \text{P} \) product, phosphorus, and alkaline phosphatase are significant factors. Furthermore, ROC curve analysis indicated that a high iPTH level was a predictive factor for PTG enlargement. Nakai et al.\(^{29}\) found that enlarged PTG were frequently detected at dialysis initiation, indicating the potential persistence of SHP and the need for strict management. The odds ratio calculated through multiple logistic regression analysis in the present study indicated a 39.8-fold higher risk for PTG enlargement when the iPTH level was 191 mg/dl or higher. Therefore, when the iPTH level is 191 mg/dl, three times the normal level, or higher, PTG US is recommended at an early stage.

This cross-sectional study is intended to investigate PTG enlargement and to perform biochemical examinations in patients undergoing hemodialysis at a single center. However, the correlation between patient morbidity and PTG enlargement was not investigated prospectively. Moreover, the study was limited because information was not obtained on usage of human recombinant erythropoietin various phosphorus-binding drugs, and vitamin D products. In addition, this study failed to achieve statistically significant results on the relationship between PTH levels and the degree of vascular calcification in the carotid artery on US. Furthermore, this study was limited because it was conducted with a small patient group at a single kidney dialysis center. In addition, this study could not determine if there was a direct causal relationship between PTG enlargement and serum phosphorus, calcium, \( \text{Ca} \times \text{P} \) product, and PTH levels. However, this study was different from the preceding large-scale studies in that it investigated PTG enlargement using PTG US, accurately determined the cutoff values for independent variables, and proposed standards for PTH lev-
els. Future studies should investigate the effectiveness of this PTH cutoff value, as well as serum phosphorus and calcium levels, as predictors of a PTG enlargement. Our results indicate that PTG US performed in accordance with the new PTH cutoff value reported in this study will improve the treatment of patients with chronic renal failure. Additional prospective studies are needed to diagnose PTG enlargement in patients with hemodialysis at an early stage and reduce its prevalence.

4 Conclusion

We suggest that in hemodialysis patients, PTG US should be performed when patient PTH levels are equal to or greater than 190 pg/mL. PTG US is useful tool to evaluate SHP in patients on maintenance hemodialysis even if their iPTH levels are within the currently acceptable range (<300 pg/mL).

References


