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ORIGINAL ARTICLE

# The Reasons of Eucalcemic Parathyroid Hormone Elevation After Parathyroidectomy for Sporadic Primary Hyperparathyroidism

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## Abstract

The success of sporadic primary hyperparathyroidism (SPHPT) treatment is providing normocalcemia independent from parathormone (PTH) levels after parathyroidectomy. However, the PTH levels of 7–40% cases remain elevated. We aimed to determine the timing of the postoperative elevation of PTH, and the relation with type of the operation, preoperative vitamin D levels, and season of the operation. Medical records of 119 SPHPT patients were reviewed retrospectively. For the purpose of the study, 99 patients were appropriate. The study is performed in Izmir, Turkey, and surrounding regions. The patients are grouped as operated on summer-spring and winter-autumn based on the sun exposure. On preoperative, postoperative 1st day, 1st week, 3rd month, 6th month, 12th month PTH levels, calcium, and vitamin D before and a year after the operation were noted. A total of 99 patients with a mean age of 57.88 were included. Low PTH levels in the first day of the operation had significant relation with high PTH levels in the first 6 months ($p < 0.05$). On the third month, eucalcemic parathyroid hormone elevation (ePTH) reached the top level and declined to 53% and 26% in 6th and 12th month, respectively. There is no significant difference between preoperative vitamin D levels, operation type, and the season of operation time; however, ePTH was more common in patients operated in autumn-winter. Our results showed that ePTH development was unrelated with vitamin D levels, operation type, and operation season. ePTH should not be accepted as an indicator of recurrence on early follow-up of patients having appropriate medical supplementation.

**Keywords** Sporadic primary hyperparathyroidism · Eucalcemic parathyroid hormone elevation · Parathyroid gland

## Introduction

The most important criteria for success of parathyroidectomy in sporadic primary hyperparathyroidism (SPHPT) is to achieve eucalcemia after the operation. However, even if the biochemical cure is achieved, 7–40% of the cases had high serum parathormone (PTH) levels [1, 2]. The reasons for this phenomenon remains unclear but surgeons generally do not accept this as recurrence or persistence. In this study, we aimed to put forward the changes in PTH levels from time to time after the operation, and declare if this increase is associated with type of the operation, vitamin D levels, and time of the operation.

## Methods

A number of 119 cases with primary hyperparathyroidism who were diagnosed and operated between 2007 and 2012 in Izmir Katip Celebi University Ataturk Training and Research Hospital with the same surgical team were reviewed retrospectively. Cases under follow-up of less than 6 months (17 cases) and had persistent disease (3 cases) were excluded. A total number of 99 patients were appropriate for the purpose of the study. All of the cases applied from Izmir (38 north latitude) and surrounding regions are with consent forms signed by every patient. Based on the sun exposure in Izmir, patients were subgrouped as operated in spring and summer

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and in autumn and winter as groups A and B respectively. Eucalcemic parathyroid hormone elevation (ePTH) was described as normal serum calcium levels with high serum PTH levels after the operation.

Patients who had scintigraphically or radiologically located parathyroid glands were accepted as suitable and were operated as limited exploration with 2.5 cm incision under general anesthesia, and only focused on the gland that is located by the preoperative imaging methods. For cases with synchronous thyroidal pathologies or localization studies were incompatible, bilateral exploration was performed. Twenty-five cases were explored bilaterally. Macroscopically suspected parathyroid glands were excised. After the excision, significant decrease in IOPTH levels was accepted as the success of the operation. Double adenomas were diagnosed in 22 patients. Another third gland was excised and postoperative transient hypocalcemia was diagnosed in 3 patients.

Quick intraoperative PTH level (IOPTH) was measured with venous sampling just before the skin incision. IOPTH was also remeasured after the excision of the adenoma in 0 and 10 min. The decrease of > 50% of PTH level after the excision of the adenoma in 0 and 10 min was described as the success of the operation. Serum calcium level was measured with photometric Abbot Architect c 16,200 method. PTH and vitamin D levels were measured with chemiluminescence Siemens Advia Centaur Xp İmmunoassay System. Normal values were accepted as 20–80 pg/ml for 1,25 dihydroxy vitamin D; 19.8–74.9 pg/ml for PTH, and 8.4–10.2 mg/dl for calcium.

In the postoperative period, serum calcium and PTH levels were measured on the 1st day, 1st week, 3rd month, 6th month, and 12th month. Biochemical cure and recurrence were described as normocalcemia in all of the measurements and high calcium levels with a normocalcemic period of the first 6 months after the operation. Persistent disease was accepted as high postoperative levels of PTH and calcium in patients diagnosed as prominent hyperactive parathyroid adenoma with preoperative localization studies. These cases were excluded and thought to be associated with multiglandular disease. Cases with continuous high serum calcium levels were accepted as persistent disease and excluded from the study. Urine calcium level was checked before the surgery. However, postoperative urine calcium level was checked in only patients with persistent disease. No cases of benign familial hypercalcemic hypocalciuria were detected. PTH levels were compared with type and time of the operation and preoperative vitamin D levels for every time of PTH measurements.

We obtained informed consent from patients and certification from the Izmir Katip Celebi University Ataturk Training and Research Hospital Ethical Committee about the relevance of the study.

The statistical analysis was performed by SPSS 15.0 package in 95% confidence interval. The changes in PTH levels were analyzed with McNemar. PTH levels were compared with type and time of the operation, vitamin D levels using chi square and Fisher's exact test. Kruskal–Wallis H statistical analysis was used in determining the difference between the age of the patients and PTH levels. A $p$ value $< 0.05$ was accepted as significant.

## Results

The PTH levels of 1st day, 1st week, 3rd, 6th, and 12th month were statistically unrelated with the age; however; the mean age of the patients with high PTH levels in 12th month was 57.8 while the mean age was 48.9 in cases with normal PTH levels at the same time of measurement.

The mean of PTH levels measured on the first day of the operation was 28.11 ± 38.99 pg/ml. The mean of PTH levels were determined as statistically higher in measurements of the 1st week, 3rd, and 6th month ($p < 0.05$). But this difference was not significant in 12th month. ePTH was observed as a phenomenon varying from time to time with a peak in 3rd month and declined to normal levels in 12th month, only 26% of the cases. (Table 1 and Fig. 1).

Bilateral and limited exploration were performed on 25 patients (25.25%) and 75 patients (74.75%) respectively. In 63% of patients operated with bilateral exploration, PTH levels were observed as high, 9% were normal, and 27% were low in postoperative 3rd month with statistically significant difference. In cases that were operated as limited exploration, PTH levels were 76% normal and 24% were high in the 12th month and all of the cases were normocalcemic. The type of the operation did not show any significant relationship with 12th month PTH levels.

Fifty-five patients were operated in spring and summer, while 44 cases were operated in autumn and winter but the relationship between the time of the operation and PTH levels was not significant.

**Table 1** Postoperative PTH levels of the cases

| | Mean ± SD | Minimum | Maximum |
|---|---|---|---|
| 1st day PTH | 28.11 ± 38.99 | 1 | 225 |
| 1st week PTH | 135.62 ± 197.25 | 3 | 396 |
| 3rd month PTH | 116.6 ± 77.88 | 3 | 318 |
| 6th month PTH | 90.81 ± 60.47 | 16 | 242 |
| 1st year PTH | 75.98 ± 45.27 | 9.7 | 318 |

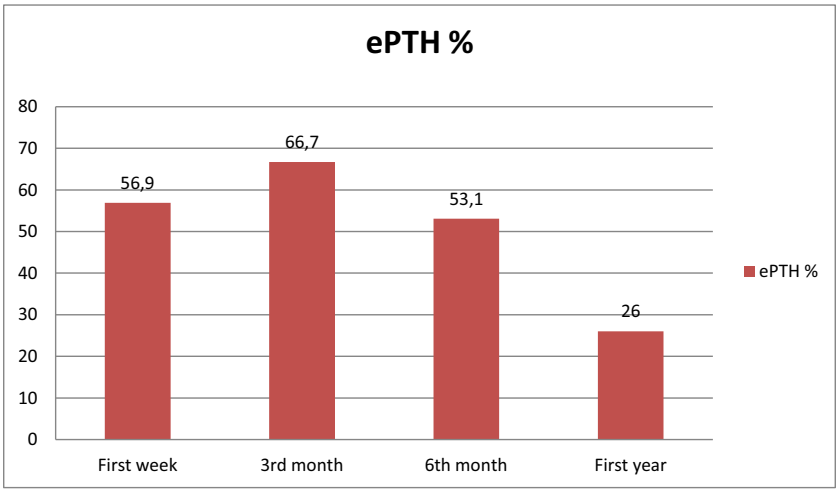


**Fig. 1** The graph of the ePTH changing over time

Preoperative vitamin D levels (1,25 dihydroxy-vitamin D) were low in 7 cases (6%) and normal and high in 92 cases (94%). The mean level of vitamin D was 54.76 ± 51.97 pg/ml. Preoperative and postoperative vitamin D levels were not statistically related to PTH levels.

## Discussion

Parathyroidectomy is the only certain solution for normalizing calcium and PTH levels in primary hyperthyroidism [3]. Fortunately, 95% of the cases were cured with first operation [4]. The decline in calcium and PTH levels to normal shows the success of the operation.

The definition of cure after parathyroidectomy is still controversial because in a significant proportion of the cases postoperative PTH levels remain high although calcium levels were normal [1, 2]. This phenomenon was called as "eucalcemic parathyroid hormone elevation" (ePTH) and the incidence were reported as 7–40%. In our study, ePTH was detected 53.1% and 26% after the 6th and 12th month of the operation respectively. There are some studies reporting as transient elevation in PTH shortly after the operation can be associated with cortical bone remineralization [5]. However, in cases with high PTH levels over a year, a residual hyperplastic parathyroidal tissue should be considered. In our study, in cases with high PTH levels, no residual parathyroidal tissue was found by high frequency ultrasonographic (USG) and scintigraphic studies (Tables 2 and 3).

Advanced age is a risk factor for ePTH. PTH levels were not statistically relevant to age; however, the mean age of the cases with high PTH levels in the 12th month of the operation is higher supporting that advanced age as a risk factor. (Table 4) In addition to that, osteoporosis, nutritional deficiencies, and the change in bone mineralization could be relevant to the risky face of the advanced age [6]. In the first 6 months period, patients' age with normal PTH and ePTH levels are similar. However, in the first year measurements, patients' mean age are 57 for ePTH and 48.9 for normal PTH levels.

Before 20 years, when the limited exploration with intraoperative PTH measurement was firstly performed, it became as the first option for sporadic primary hyperparathyroidism rather than bilateral exploration [7–12]. This depends on the success of preoperative localization methods and the power of IOPTH in verifying that the hypersecretory parathyroidal tissue is removed. Limited exploration was performed in combination with USG, scintigraphic methods, and IOPTH. Thus, during the operation, only the abnormal parathyroid glands can be excised without the need for exploration and removal of normal parathyroid glands [8–12]. In this study, limited exploration with IOPTH was compared with bilateral exploration and no significant difference was found for ePTH. However, low and high PTH levels were less common in cases operated with bilateral exploration. This could depend on the fact that in bilateral exploration the manipulation of normal parathyroid glands may affect the physiology of the glands. Larger case studies were needed for explaining the real reason.

In our study, the effect of the time of the operation on ePTH was compared according to groups operated in spring and summer in which sun exposure is higher and with autumn and winter in which sun exposure is less. ePTH was detected more common in cases operated in autumn and winter but the difference was not statistically significant. We think that sun exposure may be even less in summer due to sociocultural and nutritional conditions of our country and preoperative lack of storage for vitamin D. A larger sample in more northern areas is needed to approve the relation between postoperative parathormone elevation and time of the operation in cases operated in spring and summer. In a study planned in our region exposed that clothing habits engender to low sun exposure and insufficient vitamin D levels. The Aegean region of Turkey has a high incidence of vitamin D deficiency [13]. Vitamin D deficiency is not associated to ePTH but is associated to

**Table 2** The relationship between postoperative PTH and preoperative vitamin D levels

| | | Preoperative level of vitamin D (pg/ml) | | | Total | *p* |
|---|---|---|---|---|---|---|
| | | Low % | Normal % | High % | % | |
| P.o 1st day PTH level | Low | 100 | 46.4 | 25 | 53.9 | 0.405 |
| | Normal | – | 53.6 | 75 | 53.2 | |
| P.o 1st week PTH level | Low | – | 8.3 | – | 6.7 | 0.661 |
| | Normal | – | 41.7 | 20 | 36.7 | |
| | High | 100 | 50 | 80 | 56.7 | |
| P.o 3rd month PTH level | Low | – | 11.8 | – | 8.7 | 0.816 |
| | Normal | – | 11.8 | 25 | 13 | |
| | High | 100 | 76.5 | 75 | 78.3 | |
| P.o 6th month PTH level | Low | – | 12.5 | – | 10 | 0.904 |
| | Normal | – | 25 | 33.3 | 25 | |
| | High | 100 | 62.5 | 66.7 | 65 | |
| P.o 1st year PTH level | Low | – | 7.1 | – | 4.2 | 0.941 |
| | Normal | – | 76.9 | 65 | 69.8 | |
| | High | 100 | 16 | 35 | 26 | |

*Chi square and Fisher's exact test

*P.o* postoperative

primary hyperparathyroidism and sunlight exposure may on tribute indirectly to this phenomenon.

Some studies suggest that 17% of compensatory hyperparathyroidism is related to low postoperative vitamin D levels [2]. Despite, ePTH was described as an adaptive reaction due to renal dysfunction or vitamin D deficiency in some other studies [2]. These studies also suggest that synchronous vitamin D deficiency increases preoperative PTH levels in primary hyperparathyroidism [6]. Calcium and vitamin D replacement in early postoperative period decreases ePTH. In cases with ePTH, recurrence was reported as 3%. Vitamin D deficiency was seen more common in patients aged between 49 and 83 in northern areas with an incidence of 57% and 40% of hospitalized and outpatients, respectively [14–17]. In cases with primary hyperparathyroidism synchronous, vitamin D deficiency was common and increases the elevation of postoperative PTH levels, symptoms, and the degree of bone disease [6].

In our study, no significant relation was detected between preoperative vitamin D and postoperative PTH levels. (Table 2) Only 7 of the patients has low vitamin D levels preoperatively. Most of the patients (77 of 99) had normal and 13 has high levels of vitamin D. (Table 2) In the assessment of all patients who has preoperative low vitamin D levels were detected, that PTH levels measured as high postoperative all time periods (1st week, 3rd month, 6th month, 1st year). In the evaluation of 6th month PTH levels, high ones are composed of 100% of low preoperative vitamin D levels, 62.5% of normal preoperative vitamin D levels, and 66.7% of high preoperative vitamin D levels. Thus, situated that preoperative vitamin D levels are not associated to normocalcemic hyperparathyroidism. This may be related to postoperative empirical replacement therapy of calcium and vitamin D concerning symptomatic hypocalcemia.

In cases with low preoperative vitamin D levels, postoperative PTH levels were detected as high. But there is no statistically significance ($P > 0.05$). However, in cases with normal and high PTH levels postoperative 12th month, vitamin D levels were normal and high up to 66% of the patients. Although this appears to be conflictive with the literature, the measured form of vitamin D in our study, 1,25 dihydroxy vitamin D, gives the current status of vitamin D and this could prevent any comments about the storage of vitamin D in primary hyperparathyroidism.

In our study, more than half of the cases had low PTH levels in the first day of the operation. In a follow-up of 12 months, PTH levels remained high in half of these cases. ePTH was seen in 53.1% and 26% in 6th and 12th month follow-up of the other half of cases which had normal PTH levels in the first day of the operation. Depending on these results, cases should be under close follow-up for waiting the decrease in ePTH during a period of 1 year. And during that

**Table 3** Gender and age distribution

| Gender | *n* | Age | | | *p** |
|---|---|---|---|---|---|
| | | Mean ± SD | Minimum | Maximum | |
| Female | 86 | 57.35 ± 10.81 | 25 | 83 | 0.217 |
| Male | 13 | 61.38 ± 13.61 | 33 | 82 | |
| Total | 99 | 57.88 ± 11.22 | 25 | 83 | |

**Table 4** PTH measurements and levels comparing age

| | Low<br>Mean ± SD | Normal<br>Mean ± SD | High<br>Mean ± SD | *T*<br>Mean ± SD | *p** |
|---|---|---|---|---|---|
| 1st day PTH | 59 ± 13.08 | 57.26 ± 8.58 | | 57.9 ± 11.02 | 0.344 |
| 1st week PTH | 53.33 ± 18.72 | 59.68 ± 11.92 | 57.83 ± 11.42 | 58.25 ± 11.85 | 0.683 |
| 3rd month PTH | 66.67 ± 5,.3 | 50.88 ± 16.68 | 55.68 ± 10.81 | 55.52 ± 12.5 | 0.157 |
| 6th month PTH | 64 ± 4.24 | 52.38 ± 10.04 | 55.35 ± 11.75 | 54.69 ± 10.9 | 0.224 |
| 1st year | 61 ± . | 48.9 ± 9.73 | 57.85 ± 7.76 | 54.25 ± 9.5 | 0.058 |

*Kruskal–Wallis H analysis

time, surgeons should not worry about the recurrence especially in cases having appropriate replacement therapies.

In the conclusion, preoperative vitamin D levels and the type and the time of the operation could not be effective alone for ePTH. Also, it should be kept in mind that ePTH should not be accepted as recurrence in early postoperative period will normalize with close follow-up and appropriate replacement therapies.

## Compliance with Ethical Standards

We obtained informed consent from patients and certification from the Izmir Katip Celebi University Ataturk Training and Research Hospital Ethical Committee about the relevance of the study.

**Conflicts of Interest** The authors declare that they have no conflict of interest.

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