

Postoperative parathormone level and permanent hypoparathyroidism following total thyroidectomy: a clue for the clinician



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Postoperative parathormone level and permanent hypoparathyroidism following total thyroidectomy: a clue for the clinician

AIM: Hypoparathyroidism (HPP) is among the most commonly observed severe complications of total thyroidectomy (TT). Therefore, any permanent hypoparathyroidism (PHPP) that may develop in the postoperative period must be predicted as early as possible. This study aims to investigate the predictive value of intact parathormone (iPTH) levels on the first postoperative day after TT for PHPP.

MATERIALS AND METHODS: The study included 407 patients who underwent TT. Demographic information (sex and age), preoperative thyroid function, postoperative histopathological findings, the presence of a parathyroid gland on the pathology specimen and the length of hospital stay were recorded for all patients. iPTH and total serum calcium and albumin levels[™] were measured on the first postoperative day. According to the postoperative day 1 iPTH level (above or below 12 pg/ml), the patients were divided into two groups and compared in terms of risk factors for postoperative HPP. Patients with HPP who had low iPTH and calcium levels at the end of a 6-month follow-up were considered to have PHPP.

RESULTS: No significant differences were found between groups regarding demographic characteristics, preoperative diagnosis, type of operation and histopathological results ($p > 0.05$). The long-term follow-up of patients with HPP revealed PHPP in two patients and transient HPP in 98 patients. PHPP did not develop in patients with an iPTH level higher than 1 pg/ml on postoperative day 1. The mean time for patients to reach normal serum iPTH levels was 38.53 (± 58.22) days.

CONCLUSION: iPTH levels higher than 1 pg/ml on the first postoperative day after TT may be a clinical indicator that PHPP will not develop in these patients.

KEY WORDS: Calcium, Hypocalcaemia, Hypoparathyroidism, Total Thyroidectomy

Introduction

Total thyroidectomy (TT) is used in routine general surgical practice to treat many thyroid diseases. However, despite advancements in surgical techniques, complica-

tions may still occur. Hypoparathyroidism (HPP) is one of the most common complications seen in the early and late periods following TT¹. HPP is generally characterised by low serum parathormone (PTH) levels and correspondingly low serum calcium levels. Causes of HPP may include accidental removal of the parathyroid glands during the operation, direct damage to the parathyroid glands or ischemia in the gland caused by damage to the vessels feeding the parathyroid gland². In addition, HPP following TT may be either transient or permanent. Permanent hypoparathyroidism (PHPP) is most commonly defined as the failure of the parathyroids to regain normal function within 6 months of surgery³. Previous studies have reported transient HPP (THPP) rates of 0.19-38% and PHPP rates of 0-3%⁴.

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PHPP manifests with severe symptoms such as tetany, convulsion, and laryngeal spasm due to hypocalcaemia. In PHPP, long-term calcium and vitamin D replacement may be required to maintain normal serum calcium levels⁵. In addition, PHPP increases the risk of mortality, renal complications, myocardial dysfunction, dental abnormalities and basal ganglia calcifications⁶⁻¹⁰. Therefore, early prediction of any PHPP that may develop in the postoperative period is important for providing effective patient treatment and follow-up. Currently, there are no clearly defined parameters for the risk of PHPP during the early postoperative period after TT. On the other hand, since intact parathormone (iPTH) has a short turnover of 2-5 minutes, it is accepted as a possible marker to reflect parathyroid gland function¹¹. There are limited studies suggesting that the serum iPTH level may be a predictive factor for the existence of PHPP during the early postoperative period^{12,13}. The long-term significance of a low iPTH level after surgery for the patient has also not been elucidated. When can recovery be anticipated, and what are the

chances of developing PHPP? Therefore, our study aimed to investigate the value of iPTH level in predicting PHPP on the first postoperative day after TT.

Material and Methods

This retrospective study included all patients who underwent TT performed by experienced surgeons between January 2015 and March 2021 at the Adana City Training and Research Hospital's General Surgery Clinic. The following groups were excluded from the study: unilateral lobectomies, complementary relapse thyroidectomies, thyroidectomies performed with a parathyroid operation and patients who did not attend the control visit with postoperative HPP. All surgical procedures were performed under general anaesthesia, and lateral or central lymph node dissection was added to the TT as necessary, depending on the patient's preoperative and intraoperative findings.

In all operations, efforts were made to identify and pro-

TABLE I - Demographic, clinical and laboratory parameters of patients with and without hypoparathyroidism.

	Total n: 407 (%)	HP n:100 (%)	Non-HP n:307	p
Age, mean, year (\pm SD)	49.62(\pm 13.07)	50.14(\pm 13.36)	49.45(\pm 12.99)	0,657
Gender				0,652
Male	84 (20.6)	19 (19)	65 (21,2)	
Female	323 (79.4)	81 (81)	242(78,8)	
Preoperative Diagnosis				0,321
Nodular Goiter	231 (56.8)	51(51)	180(58,6)	
Hyperthyroidism	42(10.3)	10(10)	32(10,4)	
Malignancy	134 (32.9)	39(39)	95(39)	
Operation				0.713
TT	380 (93,4)	95(95)	285(92.8)	
TT+CLND	23 (5.7)	4(4)	19(6.2)	
TT+LLND	4(1)	1(1)	3(1)	
Corrected Total Ca ⁺⁺ , mg/dl (Postoperative first day)				<0.0001
\geq 8.5	173 (42.5)	21(21)	152(49,5)	
7.5-8.5	187 (45.9)	50(50)	137(44.6)	
<7.5	47 (11.5)	29(29)	18(5.9)	
Histopathology				0,160
Benign	256(62.9)	57(57)	199(64.8)	
Malignancy	151 (37.1)	43(43)	108(35.2)	
Number of Parathyroid removed				0,032
0	333 (81.8)	72(72)	261(85)	
1	62(15,2)	23(23)	39(12.7)	
2	10 (2.5)	4(4)	6(2)	
3	2(0.5)	1(1)	1(0,3)	
Thyroiditis				0,926
Yes	95 (23.3)	23(23)	72(23,5)	
No	312 (76.7)	77(77)	235 (76.5)	
Length of hospital stay mean, day (SD)	2.64 (\pm 0.98)	3.16(\pm 1.20)	2.48(\pm 0,84)	<0.0001

SD: Standard Deviation; TT: Total Thyroidectomy; CLND: Central Lymph Node Dissection; LLND: Lateral Lymph Node Dissection; Ca: Calcium.

tect N. Recurrent and parathyroid glands, which is standard procedure in our clinic during surgery. In addition, suturing and energy-based devices were used in combination for haemostasis as per standard procedures. After haemostasis was adequately performed, one or two drains were placed in the operative field.

The drains were removed during the postoperative period once the drainage dropped below 25 cc/day. In addition, demographic features, preoperative diagnosis, whether central or lateral neck dissection was performed with TT, postoperative histopathological results, presence of thyroiditis, number of incidentally resected parathyroid glands in the resection material and length of hos-

pital stay were recorded. PTH, total serum calcium and albumin and phosphorus levels™ were measured in all patients on postoperative day 1. iPTH was measured by a chemiluminescent immunoassay (Beckman Coulter DXI 800), with an iPTH level < 12 pg/ml being considered HPP (normal laboratory range 12-65 pg/ml) and a serum calcium level < 8.5 mg/dl being considered hypocalcaemia. Oral calcium carbonate-vitamin D support was initiated in patients who developed hypocalcaemia, and intravenous 10% calcium gluconate was given to patients presenting with symptoms such as numbness around the lips and fingertips, Chvostek and Trousseau sign.

TABLE II - Characteristics of patients with hypoparathyroidism whose iPTH levels under and above 1pg/ml

	iPTH: <1pg/ml n:25 (%)	iPTH: >1 pg/ml n:75 (%)	P
Age, mean, year (±SD)	44.40(±14.98)	52.05(±12.30)	0.012
Gender			0,659
Male	4 (16)	15 (20)	
Female	21 (84)	60(80)	
Preoperative Diagnosis			0,082
Nodular Goiter	8(32)	43(57,3)	
Hyperthyroidism	4(16)	6(8)	
Malignancy	13(52)	26(34.7)	
Operation			0.220
TT	23(92)	72(96)	
TT+CLND	1(4)	3(4)	
TT+LLND	1(4)	0(0)	
Corrected Total Ca++, mg/dl (Postoperative first day)			0.913
≥8.5	6(24)	15(20)	
7.5-8.5	12(48)	38(50.7)	
<7.5	7(28)	22(29.3)	
Histopathology			0,130
Benign	11(44)	46(61.3)	
Malignancy	14(56)	29(38.7)	
Number of Parathyroid removed			0,035
0	13(52)	59(78.7)	
1	9(36)	14(18.7)	
2	2(8)	2(2.7)	
3	1(4)	0(0)	
Thyroiditis			0,075
Yes	16(64)	61(81.3)	
No	9(36)	14 (18.7)	
Hypoparathyroidism			0,013
Transient	23(92)	75(100)	
Permanent	2 (8)	0(0)	
Length of hospital stay mean, day (SD)	3.20(±1.38)	3.14(±1.15)	0.940
PTH recovery time, mean, day(SD)	77.43 (±81.63)	26.60 (±42.98)	<0.0001

SD: Standard Deviation; TT: Total Thyroidectomy; CLND: Central Lymph Node Dissection; LLND: Lateral Lymph Node Dissection; Ca: Calcium.

Patients were discharged from the hospital when calcium levels returned to normal following oral calcium and vitamin D replacement. After being discharged, all patients were invited to weekly visits to measure serum calcium and iPTH levels™. When normal iPTH levels were reached, oral support was gradually discontinued. At the end of 6 months following the operation, the patient was considered to have PHPP if the serum iPTH level was below normal.

The patients were divided into two groups based on PTH levels (< 12 pg/ml and > 12 pg/ml) on postoperative day 1, and the groups were compared in terms of risk factors for HPP. In addition, patients who developed HPP on postoperative day 1 were divided into two subgroups with iPTH

tistibelow and above 1 pg/ml, and the values recorded in these groups were compared.

STATISTICAL ANALYSIS

Data were analysed using the SPSS 25 (SPSS Inc.) software package. First, a Chi-square test was used to compare categorical variables between the groups. Next, the Shapiro-Wilk normality test was used to determine the distribution of the continuous variables. Finally, the independent-sample t-test was used to compare normally distributed variables, and the non-parametric Mann-Whitney U test was used to compare continuous variables without normal distribution. A p-value < 0.05 was Results

A total of 407 patients were included in the study. HPP developed in 100 patients (19 men and 81 women) on postoperative day 1, whereas the iPTH levels of 307 patients (65 men and 242 women) on postoperative day 1 were within the normal range.

The mean age of the patients who developed HPP was 50.14 (± 13.36) years, and the mean age of those who did not develop HPP was 49.45 (± 12.99) years. No statistically significant difference was found between the two groups in terms of demographic characteristics ($p > 0.05$); (Table I).

In the HPP group, 51 (51%) patients were operated on for nodular goitre, 10 (10%) patients for hyperthyroidism and 39 (39%) patients for malignancy and/or the suspicion of malignancy. In the non-HPP group, 180 (58.6%) patients were operated on for nodular goitre, 32 (10.4%) patients for hyperthyroidism and 95 (39%) patients for malignancy and /or the suspicion of malignancy.

In the HPP group, 95 (95%) patients underwent TT, four (4%) patients underwent TT + central lymph node dissection (CLND) and one (1%) patient underwent TT + lateral lymph node dissection (LLND). In the non-HPP group, TT was performed in 285 (92.8%) patients, TT + CLND in 19 (6.2%) patients and TT + LLND in three (1%) patients. No significant difference was found between

the two groups in terms of preoperative diagnosis and the type of operation performed ($p > 0.05$); (Table I).

When the postoperative histopathology results of the patients were evaluated, benign pathology was found in 57 (57%) patients and malignant pathology in 43 (43%) patients in the HPP group. In the non-HPP group, benign pathology was found in 199 (64.8%) patients, and malignant pathology was found in 108 (35.2%) patients. Thyroiditis was detected in 23 (23%) patients in the HPP group and 72 (23.5%) patients in the non-HPP group. There was no difference between the two groups regarding these two histopathological parameters ($p > 0.05$).

When the postoperative specimens were examined, the number of incidentally resected parathyroids in the HP group was one in 23 (23%) patients, two in 4 (0.5%) patients and three in 1 (1%) patient. In the non-HP group, it was one in 39 (12.7%) patients, two in 6 (2%) patients and three in 1 (0.3%) patient. There was a statistically significant difference when the two groups were compared ($p < 0.05$). However, no difference was found between the two groups when the postoperative day 1 Ca⁺⁺ level and length of hospital stay were compared (Table I).

Regarding the division of patients in the HPP group into two subgroups based on iPTH level, 25 patients had a serum iPTH level < 1 pg/ml (Group A) and 75 patients had a level > 1 pg/ml (Group B). There was a significant difference between the two groups regarding age, the number of incidentally resected parathyroids and recovery time of iPTH ($p < 0.05$). However, there was no significant difference between the two groups in terms of gender, preoperative diagnosis, type of operation, histopathological results, postoperative day 1 Ca⁺⁺ level and length of hospital stay ($p > 0.05$; Table II). In our study, the mean recovery time of the 100 patients with postoperative HPP was 20.73 (± 16.47) days. However, when we analysed this subset of patients, the mean recovery time was 77.43 (± 81.63) days in patients with iPTH < 1 pg/ml and 26.60 (± 42.98) days in patients with iPTH > 1 pg/ml. PHPP was observed in two (0.49%) of the 407 patients included in our study. In the patients who developed postoperative HPP, PHPP was not observed in patients with iPTH > 1 pg/ml on postoperative day 1. However, PHPP was observed in two (8%) of 25 patients with iPTH < 1 pg/ml on postoperative day 1.

Discussion

In our study, PHPP was not observed in any patient whose iPTH level was higher than 1 pg/ml on the first postoperative day after TT but developed in two patients with levels < 1 pg/ml. Although PHPP after TT is not very common in clinics where thyroid surgery is performed at high volumes, it is still a significant problem

since it requires long-term treatment and follow-up and causes morbidity and mortality in the long term^{6,13}. The incidence of PHPP varies widely in the literature, with rates as high as 29.2% being reported in some studies¹⁴. PHPP was detected in two (0.49%) patients who underwent TT (n = 407) in our case series. Our results are congruent with the literature. Unfortunately, there is no clear consensus on a predictive biochemical parameter for PHPP after TT. Many parameters have been proposed in the literature, such as iPTH levels at postoperative hours 4 and 24 and the per cent decrease in iPTH level compared to preoperative levels 24 hours after the operation. In a study by Canu et al in which 285 patients were included, PHPP was detected in 14 (4.91%) patients. They reported the cut-off value for PTH measured on postoperative day 1 as 6.3pg/ml (the lowest measurable PTH value)¹⁵. In addition, some predictive factors have been proposed, such as the decrease in calcium levels 24 hours after operation compared to preoperative levels^{12,14,16}. On the other hand, we believe that the iPTH level measured on the first postoperative day may be a good predictor for PHPP development due to the parathormone's rapid turnover (2-5 minutes). Julian et al, Wang et al and Canugl et al previously reported critical iPTH values at postoperative hour 24, which are not very clear^{12,16,17}. In our study, PHPP was not observed in patients with iPTH levels > 1 pg/ml at postoperative hour 24. On the other hand, PHPP was observed in 8% of patients with levels < 1 pg/ml. We believe that this finding is valuable in determining the desired patient group.

Many risk factors have been identified for HPP after TT, including malignancy, thyroid gland size, lymph node dissection performed in addition to TT, incidental resection of the parathyroid gland or glands and Graves' disease^{18,19}.

In addition, Imga NN et al reported that age, large thyroid volume, thyroid carcinoma, and incidental parathyroidectomy are risk factors for postoperative HPP²⁰. Although these factors seem to differ, one that most surgeons agree on as important in preventing postoperative HPP is the identification and preservation of the parathyroid glands during the operation and preservation of the vessels feeding the parathyroid glands. In this study, accidental removal of the parathyroid glands was the only risk factor for HPP after TT. However, lymph node dissection performed in addition to TT was not a risk factor for HPP, likely because experienced surgeons performed these operations.

There is no clear consensus in the literature regarding the duration for the development of PHPP after TT. A low serum parathormone level persists for more than 6 months after TT is taken as a reference point in European guidelines, while this period is 1 year in American guidelines^{21,22}. Due to variations in the recovery period of HPP, many different durations have been reported in previous studies. Kim et al. reported an aver-

age recovery time of 27.6 ± 2.9 months in PHPP patients in their case series²³, while in the series reported by Villarroya-Marquina et al, 142 patients had postoperative HPP, with 73 of these patients recovering within 6 months, 21 recovering within 6-12 months and 12 after 1 year²⁴. In our study, the mean recovery time of 100 patients with postoperative HPP was $20.73 (\pm 16.47)$ days. Among these patients, the mean recovery time was $77.43 (\pm 81.63)$ days in patients with iPTH < 1 pg/ml and $26.60 (\pm 42.98)$ days in patients with iPTH > 1 pg/ml. Our study found that iPTH levels higher than 1 pg/ml on postoperative day 1 may be a clinical indicator that PHPP will not develop after TT. Hypocalcemia due to HPP is a severe complication after TT. Therefore, these patients require closer follow-up and treatment. In our study, PHPP was not detected in patients with a PTH value > 1pg/ml on the postoperative 1st day. According to our study, patients with a PTH value > 1pg/ml on the postoperative 1st day seem to be less likely to develop PHPP.

Therefore, we argue that patients with a PTH value of <1pg/ml on postoperative day 1 should be followed more closely. Based on our clinical experience, we believe that PHPP will not develop if the iPTH level is 0-1 pg/ml (measurable PTH). Unfortunately, we could not provide rigorous evidence for this hypothesis because our hospital laboratory cannot measure iPTH levels < 1 pg/ml. Furthermore, we think this trend is independent of conditions such as Graves' disease, thyroid cancer and central-lateral neck dissection, which have been reported as risk factors for PHPP in previous studies. In other words, no matter what operation is performed, we believe that PHPP will not develop if the iPTH level is > 1 pg/ml on the first postoperative day. On the other hand, a study by Promberger et al. reports eight cases where PHPP developed in spite of normal iPTH levels after a 1-year follow-up period.

This may be explained as an inadequate parathyroid response to hypocalcaemia, and it is reportedly more correct to call this entity 'parathyroid insufficiency' than HPP. Based on our findings and clinical experience²⁵. However, we are aware that our study has some limitations. First, it is a retrospective study with small sample size. In addition, we estimate that the parameters mentioned above may be affected by regional, genetic and racial factors.

Conclusion

Many risk factors have been identified in the literature for HPP after TT. Although these factors seem to differ, in daily practice, most surgeons agree that the essential factor in avoiding postoperative HPP is identifying and preserving the parathyroid glands during the operation and preserving the vessels feeding the parathyroid glands. Our findings suggest that an iPTH level of more

than 1 pg/ml on the first postoperative day after TT may be a clinical indicator for not developing PHPP. However, additional prospective, randomised, controlled clinical studies are needed to reach definitive conclusions in this regard.

Riassunto

L'ipoparatiroidismo (HPP) è tra le complicanze gravi più comunemente osservate della tiroidectomia totale (TT). Pertanto, l'eventuale ipoparatiroidismo permanente (PHPP) che può svilupparsi nel periodo postoperatorio deve essere previsto il prima possibile. Questo studio mira a studiare il valore predittivo dei livelli di paratormone intatto (iPTH) nel primo giorno postoperatorio dopo TT per PHPP.

Lo studio ha incluso 407 pazienti sottoposti a TT. Per tutti i pazienti sono state registrate le informazioni demografiche (sesso ed età), la funzionalità tiroidea preoperatoria, i reperti istopatologici postoperatori, la presenza di una ghiandola paratiroidea sul campione patologico e la durata della degenza ospedaliera. L'iPTH e i livelli sierici totali di calcio e albumina sono stati misurati il primo giorno postoperatorio. In base al livello di iPTH postoperatorio al giorno 1 (superiore o inferiore a 12 pg/ml), i pazienti sono stati divisi in due gruppi e confrontati in termini di fattori di rischio per l'HPP postoperatorio. I pazienti con HPP che avevano bassi livelli di iPTH e calcio alla fine di un follow-up di 6 mesi sono stati considerati affetti da PHPP.

RISULTATI: non sono state riscontrate differenze significative tra i gruppi per quanto riguarda caratteristiche demografiche, diagnosi preoperatoria, tipo di intervento e risultati istopatologici ($p > 0,05$). Il follow-up a lungo termine dei pazienti con HPP ha rivelato PHPP in due pazienti e HPP transitorio in 98 pazienti. PHPP non si è sviluppato in pazienti con un livello di iPTH superiore a 1 pg/ml il giorno postoperatorio 1. Il tempo medio per i pazienti per raggiungere livelli sierici L di iPTH superiori a 1 pg/ml il primo giorno postoperatorio dopo TT possono essere un indicatore clinico del fatto che PHPP non si svilupperà in questi pazienti.

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