RESEARCH ARTICLE

Effect of incidental parathyroidectomy on postoperative calcium levels after total thyroidectomy

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Abstract

Background: Incidental parathyroidectomy during total thyroidectomy may occur even in the most experienced hands. This study aims to assess the incidence, risk factors, and impact of incidental parathyroidectomy on this very targeted group of patients.

Methods: Three hundred and four consecutive cases undergoing total thyroidectomy in a tertiary referral center were prospectively studied. Based on the histopathology report, incidental parathyroidectomy was assessed in relation to postoperative transient/permanent hypocalcemia. Demographic, clinical, and histological data were analyzed.

Results: The overall incidence of unintentional removal of parathyroid glands during total thyroidectomy was 35.5 %. Indicators were the postoperative hypocalcemia, the percent change of parathormone serum levels, and the presence of lymph nodes in the histopathology report. Patients with incidental parathyroidectomy exhibited a higher incidence of transient hypocalcemia and hypoparathyroidism postoperatively.

Conclusions: Incidental parathyroidectomy is associated with transient hypocalcemia after total thyroidectomy. Even single parathyroid in the histopathology specimen may be sufficient for influencing postoperative PTH levels and calcium. Every effort should be made by surgeons to identify and protect all parathyroid glands successfully. HIPPOKRATIA 2020, 24(2): 72-76.

Keywords: Incidental parathyroidectomy, total thyroidectomy, postoperative hypocalcemia, postoperative hypoparathyroidism, parathyroid glands

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Introduction

Hypoparathyroidism constitutes the most common complication of thyroidectomy and is typically related to trauma, devascularization, or accidental excision of parathyroids during the procedure[1,2]. Postoperative hypoparathyroidism leads to hypocalcemia, which is typically transient[3,4]. However, it may seriously affect the postoperative quality of life and length of hospitalization[4,5]. Occasionally, hypocalcemia may become very serious and even life-threatening, or permanent, requiring life-long strenuous efforts to manage calcium blood levels with medications[6,7].

While every effort should be made by the surgeon to identify and protect all parathyroids successfully, they still appear occasionally on the pathology report even in the most experienced hands[8,9]. Incidental parathyroidectomy (IP) rates vary widely among reports in the literature[10]. The exact effect of IP and the number of removed parathyroid glands on the postoperative calcium blood levels has not been extensively studied. Recuperation of patients following thyroidectomy is still not clear[11-15], mainly due to the studied population's heterogeneity and offered procedures. Overall, data on incidental parathyroidectomy after total thyroidectomy (TT) are scarce in the literature.

This study aims to prospectively assess the incidence and factors associated with incidental IP in cases undergoing TT strictly. Subsequently, to evaluate its effect on the postoperative calcium serum levels.

Materials and Methods

Data were prospectively collected for all patients who undergone TT at the tertiary Department of Otorhinolaryngology of Heraklion, Crete between July 2015 and June 2017. Patients received during hospitalization the standards of care according to institutionally approved protocols, signed informed consent for thyroid surgery. As all data analyzed were those of routine thyroid surgery, the institutional review board waived the need for additional consent. The same surgical team performed all surgical procedures. We defined as TT a total, extracapsular thyroidectomy. We excluded from the study patients

with renal failure, concomitant parathyroid disease, and patients in whom TT was offered as part of another oncologic procedure i.e., total laryngectomy. IP was defined as the presence of parathyroids on permanent histology and was assessed in relation to the postoperative transient or permanent hypocalcemia. Additional data collected included patient age, gender and co-morbidities, perioperative parathyroid hormone (PTH) levels, central compartment lymph node dissection, number and position of parathyroid glands identified in the surgical specimen, and histologic diagnosis.

Preoperative total serum calcium, phosphate, magnesium, and albumin were measured for every case using standard laboratory methods (Advia 1800 Chemistry System, Siemens Healthineers, Germany). Albumin-corrected calcium was calculated according to the formula:

"Corrected calcium" = serum calcium + 0.8 x (4 - serum albumin)

Postoperative serum calcium was monitored every twelve hours until three consecutive measurements within the normal values of calcium were obtained, and patients were discharged. In addition, the PTH level was measured in every patient on the first postoperative day. Normal values of calcium were considered between 8.0 and 10.6 mg/dl. Hypocalcemic patients received oral supplementation therapy, even if asymptomatic when the level of calcium was between 7.5 to 8.0 mg/dl. Oral supplementation therapy was in the form of oral calcium carbonate, 3 g per day (1 g every 8 hours), alfacalcidol, 1 μg every 8 hours, and magnesium pidolate. Intravenous (IV) calcium gluconate in the form of infusion was administered to the patients, together with an oral supplementation regimen, if serum-corrected calcium levels were below 7.5 mg/dl (20 ampules of calcium gluconate in 1 Lt of normal saline, 40 ml/h). Permanent hypocalcemia was defined as hypocalcemia requiring medical supplementation for more than six months after surgery.

Table 1: Demographic and clinical characteristics of the 304 consecutive patients who underwent total thyroidectomy in our tertiary referral center and were prospectively assessed.

Characteristic	
Age (years)	51 ± 14
Females	215 (70.5)
Thyroid cancer	166 (54.4)
Lymph nodes present in histology	13 (4.3)
Parathyroid glands present in histology	108 (35.5)
Preoperative calcium (mg/dL)	9.3 (9.1-9.5)
Postoperative calcium (mg/dL)[1]	8.6 (7.9-9)
Percentage of Calcium change	7 (4.2-12)
Postoperative hypocalcaemia[2]	84 (27.6)
Preoperative PTH (pg/mL)	65.3 (48-83.1)
Postoperative PTH (pg/mL)	34 (13.6-50)
Percentage of PTH change	48.1 (21-77)

Values are expressed as mean ± standard deviation, number of patients with percentage in brackets, or median with interquartile range in brackets, [1]: the lowest post-operative serum calcium during hospitalization, PTH: parathyroid hormone, [2]: defined as Calcium <8 mg/dL.

Data analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Patients with parathyroid glands present in histology, e.g., IP after TT, were compared with patients without any parathyroid glands present in histology. Categorical variables were compared between the two groups using the chi-squared test or Fisher's exact test. Mean [standard deviation (SD) in brackets] was used as a summary statistic for normally distributed variables and median [interquartile range (IQR) in brackets] for non-normally distributed variables. Differences in PTH percent change [100 x (preoperative-postoperative)/preoperative PTH] between groups were tested with non-parametric tests (Mann-Whitney U and Kruskal-Wallis tests). For significant associations in the univariate analysis, we estimated odds ratio (OR) or beta [95 % confidence interval (95 %CI)] with logistic or linear regression modes, respectively, adjusting for gender and age.

Results

Overall, 304 patients underwent TT with a mean age of 51 years, of whom the majority were females (70.5 %). Population characteristics are shown in Table 1. Malignancy (thyroid cancer) was confirmed histologically in 166 (54.4 %) patients, and lymph nodes were present in 13 (4.3 %) histology samples. A total of 108 cases (35.5 %) had parathyroids present on histology. Of them, 93 patients had one parathyroid gland unintentionally removed during the procedure, while 15 had at least two. Among a total of 124 parathyroids present on histology, 79 (63.7 %) were extracapsular and 45 (36.3 %) intracapsular. No glands were reported to be surrounded entirely by thyroid parenchyma.

Postoperatively there was a median 48.1 (IQR: 21.0-77) % change in PTH and 7 (4.2-12) % change in calcium levels. Postoperative hypocalcaemia (<8.0 mg/dL) occurred in 84 (27.6 %) subjects of whom 11 (3.6 %) patients had severe hypocalcaemia (<7.5 mg/dL) and required both oral and IV supplementation.

Table 2 presents the associations of parathyroid gland presence in histology with TT related factors as given by univariate analysis. IP was significantly associated with postoperative hypocalcaemia (OR: 5.0, 95 %CI: 2.9-8.6, p <0.001) and with higher drop in PTH (% change PTH: beta: 22.5 (95 %CI: 16.5-30.6, p <0.001). The presence of lymph nodes in histology was also associated with a higher risk for concomitant IP (OR: 4.2, 95 %CI: 1.3-14.2, p =0.019). There was no significant association of IP with malignancy. Surprisingly, when we compared one with at least two parathyroid glands in histology, there were no significant differences between the groups (Table 3).

Table 2: Thyroidectomy-related factors associated with incidental parathyroidectomy.

	Parathyroids absent in histology n =196	Parathyroids present in histology n =108	p*
Lymph nodes present in histology	4 (2.1)	9 (8.3)	0.016
Thyroid cancer; n (%)	104 (53.1)	62 (57.4)	0.543
Postoperative hypocalcemia[1]	31 (15.9)	52 (48.1)	<0.001
Percentage of PTH change	35.5 (11.7-59.2)	76 (46-94)	<0.001

Values are expressed as number of patients with percentage in brackets, or median with interquartile range in brackets, [1]: defined as Calcium <8 mg/dL, *: p-value is given by chi-square or Fisher's exact test for binary outcomes or Mann-Whitney U test for continues outcomes, PTH: parathyroid hormone.

Table 3: Thyroidectomy-related factors associated with the number of parathyroid glands in histology specimens.

	One parathyroid in histology n =93	At least 2 parathyroids in histology n =15	p*
Lymph nodes present in histology	7 (7.5)	1 (13.1)	0.609
Thyroid cancer	53 (57.0)	5.4 (60.0)	0.999
Postoperative hypocalcaemia[1]	44 (47.3)	8 (53.3)	0.877
Percentage of PTH change	76.1 (45.5-94.0)	72.8 (40.9-95.1)	0.893

Values are expressed as number of patients with percentage in brackets, or median with interquartile range in brackets, 1: defined as Calcium <8 mg/dL, *: p-value is given by chi-square or Fisher's exact test for binary outcomes or Mann-Whitney U test for continues outcomes, PTH: parathyroid hormone.

Six months after surgery, only four patients (1.31 %) remained under oral calcium supplementation. These cases had parathyroids present on histology; three had one and one had two glands removed. Malignancy was present in two cases, and a lymph node dissection was performed in one. Numbers were too low to be further evaluated.

Discussion

Thyroidectomy represents the most significant endocrine surgical procedure. Its modern era was introduced by Theodore Kocher, and it has since evolved into an effective and safe operation with minimal morbidity and negligible mortality[16]. However, postoperative hypoparathyroidism remains a significant cause of concern as it represents the most common major complication of thyroidectomy. The reported incidence varies widely among studies, ranging from 16 to 55 %. Most hypoparathyroidism cases are mild and easily controlled with oral calcium supplementation. Still, some may become severe or even life-threatening, requiring careful monitoring and intravenous supplementation for extended periods of time. It has been repeatedly shown that postoperative hypocalcemia is a significant factor leading to a prolonged hospital stay and increased patient discomfort following thyroidectomy[6,7]. Postoperative hypoparathyroidism may be considered transient or permanent when calcium supplementation lasts, accordingly, for less or more than six months.

Several studies in the literature have attempted to explore the incidence and clinicopathological characteristics of incidental parathyroidectomy[8,9,11,12,14,17-20]. In a systematic review conducted by Bai et al, the average IP incidence was estimated to be 12.4 % with a wide range from 2.9 % to 31 %[10]. In this study, IP was remarkably high, reaching 35.5%. At first sight, the results may cause some surprise, though, might be easily justified if we more closely examine the studied population. All cases in the current study underwent TT, and this is the standard operation offered for thyroid diseases in our center. A central neck lymph node dissection is additionally performed in malignancy whenever the central neck compartment is involved based on the preoperative radiologic evaluation or the intraoperative findings. On the contrary, most published studies reporting on IP are comprised of cases in which all different types of thyroid operations were performed[8,9,19,21].

TT refers to removing all visible thyroid tissue and significantly differs from lobectomy, subtotal, and near-total thyroidectomy as a procedure. The two upper parathyroids' position is fairly consistent, with the superior thyroid pole and the cricothyroid junction being the most common sites. The lower parathyroids show a wider topographic variation and may be found more frequently in ectopic location[15]. Due to their typically intimate anatomic relation to the thyroid gland, their small size, and unimpressive appearance, in addition to variations in location and number, parathyroid glands are vulnerable to iatrogenic trauma during thyroid surgery. During TT, the surgeon will inevitably encounter the dorsal part of both thyroid lobes, and consequently all parathyroid glands.

It has been previously shown that TT significantly increases the risk of unintentional removal of parathyroid glands. Bai et al reported that the rate of IP in TT was

57.2 %[10]. Furthermore, TT is a well-known risk factor for postoperative hypocalcemia and hypoparathyroidism[22]. This study confirms that IP is a considerable event in patients undergoing TT and highlights the impact of IP on the patient's postoperative course of PTH and calcium. Moreover, this study's results suggest that even single parathyroid in the histopathology specimen may be sufficient for influencing postoperative PTH levels and calcium.

The effect of IP on postoperative calcium and PTH serum level has attracted much attention lately. Several studies in the literature support that IP is associated with postoperative hypocalcemia transient or permanent and vice versa[8-11,17-19,21]. The existing variety among studies of postoperative hypocalcemia transient and/or permanent definitions, the extent of the procedure included, and incidence of IP might explain the conflicting data obtained on this topic. Lin et al reviewed 3,186 thyroidectomies and found an increased incidence of temporary as well as permanent hypocalcemia in IP cases[8]. In the previous study, IP on the histopathology report significantly increased the risk of permanent hypoparathyroidism. Another high volume center demonstrated that IP was associated with temporary but not with permanent hypocalcemia or hypoparathyroidism[9].

In this study, postoperative hypocalcemia occurred in 27.6 % of patients, while a drop of PTH serum levels of 48.1 % was observed. Subjects with IP exhibited significantly increased transient postoperative hypocalcemia. Moreover, IP was related to PTH's significant decline, which we have previously reported to be a reliable predictor for the occurrence and severity of hypocalcemia[5]. Only four cases in this study developed permanent hypoparathyroidism and required oral supplementation for more than six months. In contrast to other studies, when the number of parathyroid glands present in histopathology specimens was assessed, it was not associated with postoperative hypocalcemia and PTH drop. Therefore, we can hypothesize that the presence of at least one parathyroid in histology increases the risk of postoperative hypocalcemia, but this is not further affected by a higher number of parathyroids in the specimen. However, the cases with more than one parathyroid gland were limited (n =15), and more research is needed to draw safe conclusions.

Several risk factors for IP have been proposed in previous reports[8,10,13,17,20], but evidence remains controversial. Pooled data from a meta-analysis showed that central node dissection, malignancy, TT, and reoperation are independent risk factors for IP[10]. In a large case series, Lin et al[8] demonstrated that TT, central node dissection and reoperation increased the likelihood of unintentional removal of parathyroid glands. Malignancy was significantly higher in patients with IP on univariate analysis, but not an independent risk factor after multiple regression analysis[8]. In a large cohort, Prazenica et al[9], showed that the type of surgery and Graves diseases were risk factors and not malignancy. Consistent with previous studies, lymph nodes on histology, but not malignancy, increased the likelihood of IP in the current study (Table 2). Since TT was the only offered procedure, malignancy with or without lymph node dissection was the single disease-related variable analyzed. Furthermore, postoperative hypocalcemia and percent of PTH drop could be accurately predicted by the presence of parathyroid glands in the histopathology specimens.

Concerning the location of the unintentionally excised parathyroid glands, inconsistency exists among different studies[10]. Our results are in accordance with the two largest cohort studies, in which the majority of glands were either extracapsular or intracapsular[8,9]. In the current study, 63.8 % of the excised parathyroids were found outside the thyroid gland and capsule, while 36.2 % were outside the thyroid parenchyma but surrounded by the thyroid capsule. Surprisingly, no parathyroid tissue was found to be completely enclosed within the thyroid gland in this cohort, though the incidence of intrathyroidal location ranges from 2.2 % to 50 % in the literature[10]. Our results agree with cadaveric studies reporting that only 0.2 % of the population have glands completely surrounded by thyroid tissue[23,24]. Therefore, we can hypothesize that good knowledge of anatomy, accurate identification, and preservation of parathyroids might significantly reduce IP incidence.

Up until now, the majority of published data on IP was obtained by retrospective analyses[25-29]. This study's prospective nature limits the potential sources of bias and overcomes the relatively small sample size of the study. The fact that only cases with TT were included minimizes selection bias.

Our data suggests that IP is a considerable event in patients undergoing TT and confirms the impact of IP on patients' postoperative course. Notably, the presence of even one parathyroid gland in histopathology specimen is significantly associated with transient postoperative hypocalcemia. Therefore, every effort should be made to meticulously dissect, identify, and preserve the parathyroid glands during thyroid surgery. IP and postoperative hypocalcemia rate, may lead to bothersome and even dangerous symptoms and significantly increase the length, and cost of hospitalization. In-depth anatomical knowledge related to variations and adequate training is of great importance to minimize the risk of transient and permanent hypoparathyroidism.

Conflict of interest

None declared by authors.

References

1. Gourin CG, Tufano RP, Forastiere AA, Koch WM, Pawlik TM, Bristow RE. Volume-based trends in thyroid surgery. Arch Otolaryngol Head Neck Surg. 2010; 136: 1191-1198.
2. Hallgrimsson P, Nordenström E, Bergenfelz A, Almquist M. Hypocalcaemia after total thyroidectomy for Graves' disease and for benign atoxic multinodular goitre. Langenbecks Arch Surg. 2012; 397: 1133-1137.
3. Mitchell DM, Regan S, Cooley MR, Lauter KB, Vrla MC, Beck-

er CB, et al. Long-term follow-up of patients with hypoparathyroidism. J Clin Endocrinol Metab. 2012; 97: 4507-4514.
4. Sitges-Serra A, Ruiz S, Girvent M, Manjón H, Dueñas JP, Sancho JJ. Outcome of protracted hypoparathyroidism after total thyroidectomy. Br J Surg. 2010; 97: 1687-1695.
5. Karatzanis AD, Ierodiakonou DP, Fountakis ES, Velegrakis SG, Doulaptsi MV, Prokopakis EP, et al. Postoperative day 1 levels of parathyroid as predictor of occurrence and severity of hypocalcaemia after total thyroidectomy. Head Neck. 2018; 40: 1040-1045.
6. Marcus B, Edwards B, Yoo S, Byrne A, Gupta A, Kandrevas J, et al. Recurrent laryngeal nerve monitoring in thyroid and parathyroid surgery: the University of Michigan experience. Laryngoscope. 2003; 113: 356-361.
7. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg. 2014; 101: 307-320.
8. Lin YS, Hsueh C, Wu HY, Yu MC, Chao TC. Incidental parathyroidectomy during thyroidectomy increases the risk of postoperative hypocalcemia. Laryngoscope. 2017; 127: 2194-2200.
9. Praženica P, O'Driscoll K, Holy R. Incidental parathyroidectomy during thyroid surgery using capsular dissection technique. Otolaryngol Head Neck Surg. 2014; 150: 754-761.
10. Bai B, Chen Z, Chen W. Risk factors and outcomes of incidental parathyroidectomy in thyroidectomy: A systematic review and meta-analysis. PloS One. 2018; 13: e0207088.
11. Lee NJ, Blakey JD, Bhuta S, Calcaterra TC. Unintentional parathyroidectomy during thyroidectomy. Laryngoscope. 1999; 109: 1238-1240.
12. Sakorafas GH, Stafyla V, Bramis C, Kotsifopoulos N, Kolettis T, Kassaras G. Incidental parathyroidectomy during thyroid surgery: an underappreciated complication of thyroidectomy. World J Surg. 2005; 29: 1539-1543.
13. Sippel RS, Ozgül O, Hartig GK, Mack EA, Chen H. Risks and consequences of incidental parathyroidectomy during thyroid resection. ANZ J Surg. 2007; 77: 33-36.
14. Spiliotis J, Vaxevanidou A, Sergouniotis F, Tsiveriotis K, Datsis A, Rogdakis A, et al. Risk factors and consequences of incidental parathyroidectomy during thyroidectomy. Am Surg. 2010; 76: 436-441.
15. Bergamaschi R, Becouarn G, Ronceray J, Arnaud JP. Morbidity of thyroid surgery. Am J Surg. 1998; 176: 71-75.
16. Gourgiotis S, Moustafellos P, Dimopoulos N, Papaxoinis G, Baratsis S, Hadjiyannakis E. Inadvertent parathyroidectomy during thyroid surgery: the incidence of a complication of thyroidectomy. Langenbecks Arch Surg. 2006; 391: 557-560.
17. Youssef T, Gaballah G, Abd-Elaal E, El-Dosoky E. Assessment of risk factors of incidental parathyroidectomy during thyroid surgery: a prospective study. Int J Surg. 2010; 8: 207-211.
18. Ozoğul B, Nuran Akçay M, Kisaoğlu A, Atamanalp SS, Oztürk G, Aydinli B. Incidental parathyroidectomy during thyroid surgery: risk factors, incidence, and outcomes. Turk J Med Sci. 2014; 44: 84-88.
19. Manouras A, Markogiannakis H, Lagoudianakis E, Antonakis P, Genetzakis M, Papadima A, et al. Unintentional parathyroidectomy during total thyroidectomy. Head Neck. 2008; 30: 497-502.
20. Erbil Y, Barbaros U, Ozbey N, Aral F, Ozarmağan S. Risk factors of incidental parathyroidectomy after thyroidectomy for benign thyroid disorders. Int J Surg. 2009; 7: 58-61.
21. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. Am J Surg. 2006; 191: 418-423.
22. Wingert DJ, Friesen SR, Iliopoulos JI, Pierce GE, Thomas JH, Hermreck AS. Post-thyroidectomy hypocalcemia. Incidence and risk factors. Am J Surg. 1986; 152: 606-610.
23. Akerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. Surgery. 1984; 95: 14-21.
24. Taterra D, Wong LM, Vikse J, Sanna B, Pękala P, Walocha J, et al. The prevalence and anatomy of parathyroid glands: a meta-analysis with implications for parathyroid surgery. Langenbecks Arch Surg. 2019; 404: 63-70.
25. Neagoe RM, Cvasciuc IT, Muresan M, Sala DT. INCIDENTAL PARATHYROIDECTOMY DURING THYROID SURGERY - RISK, PREVENTION AND CONTROVERSIES; AN EVIDENCE-BASED REVIEW. Acta Endocrinol (Buchar). 2017; 13: 467-475.
26. Christakis I, Zacharopoulou P, Galanopoulos G, Kafetzis ID, Dimas S, Roukounakis N. Inadvertent parathyroidectomy risk factors in 1,373 thyroidectomies-male gender and presence of lymphadenopathy, but not size of gland, independently increase the risk. Gland Surg. 2017; 6: 666-674.
27. Alraddadi T, Aldhahri S, Almayouf M, Alharbi J, Malas M, Nasrullah M, et al. Risk Factors of Incidental Parathyroidecomy in Thyroid Surgery. Cureus 2019; 11: e6517.
28. Du W, Fang Q, Zhang X, Cui M, Zhao M, Lou W. Unintentional parathyroidectomy during total thyroidectomy surgery: A single surgeon's experience. Medicine (Baltimore). 2017; 96: e6411.
29. Praženica P, O'Keeffe L, Holý R. Dissection and identification of parathyroid glands during thyroidectomy: association with hypocalcemia. Head Neck. 2015; 37: 393-399.