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## The long-term need for calcium supplementation after incidental parathyroidectomy



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### المخلص

**أهداف البحث:** يعتبر نقص كالسيوم الدم وقصور الدريقات أكثر المضاعفات شيوعاً لاستئصال الغدة الدرقية الكلي والتي قد تؤدي إلى الحاجة إلى مكملات الكالسيوم مدى الحياة. الهدف من هذه الدراسة هو بحث تأثير استئصال الدريقات العرضي على نقص كالسيوم الدم قصير وطويل الأمد.

**طرق البحث:** أجريت هذه الدراسة الاستيعابية على المرضى الذين خضعوا لاستئصال الغدة الدرقية الكلي مع أو بدون تشريح عنق مركزي من مارس ٢٠١٦ إلى مايو ٢٠١٨. تم إجراء جميع الإجراءات من قبل ثلاثة جراحين بمستويات مماثلة من الخبرة. كما تمت مراجعة تقارير الهستوباثولوجيا، وتم تسجيل عدد الدريقات المستأصلة والتقارير الباثولوجية، وتم تقسيم المرضى إلى مجموعتين: المجموعة أ، مع وجود دريقات في العينة، والمجموعة ب، بدون دريقات. تم تسجيل معدلات حدوث نقص كالسيوم الدم على المدى القصير والطويل. وتم الحصول على الأول من خلال فحوصات الدم أثناء التنويم في المستشفى والأخير عن طريق المكالمات الهاتفية للمرضى بعد ٣ و٦ و١٢ شهراً من الجراحة.

**النتائج:** ضمت الدراسة ما مجموعه ١١٦ مريضاً، ١٨ (١٥.٥٪) في المجموعة أ، و ٩٨ (٨٤.٥٪) في المجموعة ب. لم يتم الكشف عن دلالة إحصائية بين المجموعتين فيما يتعلق بفترة ما بعد الجراحة المبكرة أو نقص كالسيوم الدم على المدى الطويل. وقد كانت النتائج مشابهة لدى مرضى السرطان وعددهم ٤٠ مشاركاً.

**الاستنتاجات:** لم يكن استئصال الدريقات العارض لدقيقة واحدة مرتبطاً بارتفاع معدل الإصابة بنقص كالسيوم الدم، حتى في حالات سرطان الغدة الدرقية.

**الكلمات المفتاحية:** استئصال الغدة الدرقية؛ قصور الدريقات؛ نقص كالسيوم الدم؛ الدريقات؛ الكالسيوم

### Abstract

**Objectives:** Hypocalcaemia and hypoparathyroidism are the most frequent complications of total thyroidectomy that may result in the need for lifelong calcium supplementation. This study aims to investigate the impact of incidental parathyroidectomy on short- and long-term hypocalcaemia.

**Methods:** This retrospective study was conducted on patients who underwent total thyroidectomy with or without central neck dissection between March 2016 to May 2018. All procedures were performed by three surgeons with similar experience levels. Histopathology reports were reviewed, the number of resected parathyroid glands and the underlying pathology reports were recorded, and the patients were divided into two groups; groups A and B comprised those with and without parathyroid glands respectively. The incidence rates of short- and long-term hypocalcaemia were recorded. The former was obtained through blood tests during hospitalisation and the latter via phone calls to patients 3, 6, and 12 months postoperatively.

**Results:** A total of 116 patients participated, 18 (15.5%) in group A and 98 (84.5%) in group B. No statistical

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significance was detected between the two groups regarding early postoperative ( $p = 0.109$ ) or long-term hypocalcaemia ( $p = 0.48$ ). These results were similar in patients with cancer ( $n = 40$ ) ( $p = 0.855$ ,  $p = 0.08$ ).

**Conclusion:** Incidental parathyroidectomy of one parathyroid gland was not correlated with a higher incidence of hypocalcaemia, even in cases with thyroid cancer.

**Keywords:** Calcium; Hypocalcaemia; Hypoparathyroidism; Parathyroid glands; Thyroidectomy

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## Introduction

Total thyroidectomy is a common surgical procedure indicated for thyroid pathologies such as cancer, goitre, Graves' disease, and nodules suspicious of malignancy. Commonly reported complications of the procedure include vocal cord palsy and bleeding, while tracheomalacia and thyrotoxic crisis are rare complications that occur when thyroid function is not regulated before the surgery.<sup>1–4</sup> However, postoperative hypocalcaemia (HYC) is by far the most common complication. The incidence rates of transient and permanent HYC requiring calcium/vitamin D supplementation have been reported to reach 50% and 1.5–4%, respectively.<sup>5–13</sup> Most cases are usually asymptomatic, and the lowest levels of calcium (Ca) should be expected within 72 hours of the surgery.<sup>4</sup>

The cause of postoperative HYC could be attributed to intraoperative ischaemia or resection of one or more parathyroid glands (PG), resulting in a decline in circulating parathyroid hormone (PTH).<sup>14,15</sup>

Questions have been raised over whether removed or devascularised PGs are the only factors responsible for postoperative HYC. For example, following thyroidectomy for Graves' disease, HYC may occur regardless of the preservation of the PG. This is a result of rapid accretion of calcium back into the bones – the “hungry bone syndrome” – since many patients with Graves' disease are osteoporotic. Their serum phosphorus level is usually normal or low, and their parathyroid function is normal. What is also paradoxical is the fact that symptoms of HYC or those simulating HYC can also occur after surgeries that are not related to the head and neck, such as cholecystectomy.<sup>2</sup>

The current study aims to examine the incidence of incidental parathyroidectomy (IP) and its correlation with clinical and laboratory HYC. Transient, protracted, and permanent hypoparathyroidism (HYP) in all patients undergoing total thyroidectomy were examined and the correlations between calcium levels in the early postoperative period and long-term HYP were analysed.

## Materials and Methods

All subjects signed an informed consent form that explained that there would be no deviation from the standard care practices. This retrospective study included all patients who underwent total/near total thyroidectomy at our institution between March 2016 to May 2018. Patients who were excluded were those with an underlying condition affecting their calcium levels, such as parathyroid adenoma, chronic renal failure, sarcoidosis, medullary carcinoma of the thyroid, and those receiving oral calcium and/or vitamin D supplementation before the surgery. Patients undergoing total thyroidectomy combined with total laryngectomy for laryngeal cancer were also excluded.

Preoperative levels of calcium, phosphorus, magnesium, and albumin were recorded in mg/dL for the electrolytes and in g/dL for albumin. Laboratory tests were repeated on the first and second postoperative days (all thyroidectomy patients were hospitalised for two postoperative days according to the standard practice of care in our institution).

All laboratory tests were normal preoperatively; therefore, no oral calcium supplementation was needed before the surgery. Calcium levels were corrected for hypoalbuminemia (less than 4 g/dl). Any clinical manifestations of HYC, such as tetania, were recorded, as was the need for calcium supplementation, whether it was oral or intravenous (IV). Patients were contacted by phone, 3, 6, and 12 months after the surgery to enquire whether they needed oral calcium supplementation. Long-term HYP is defined by either laboratory confirmation of decreased PTH levels or the need to take oral calcium/vitamin D supplementation.

Histopathologic reports of the specimens were also reviewed to confirm the presence of the parathyroid tissue, its position relevant to the thyroid (intrathyroidal, intracapsular, or extrathyroidal), and the presence of malignancy.

The parathyroid glands were routinely identified intraoperatively, and excessive manipulation was avoided whenever possible. Autologous transplantation of the PG intraoperatively was performed in only two patients. Permanent HYP is defined as the patient's need for oral calcium supplementation for at least one year. In protracted HYP, supplementation is required for at least six months, and in transient HYP, at least for three months. Preferably used oral supplementation was a combination of calcium carbonate and alfacalcidol, whereas for IV use, calcium gluconate in a solution of 250 ml D/W was preferred. Thus, for patients with mild HYC ( $\text{Ca} < 8.5$  mg/dl) in the direct postoperative period, oral supplementation was used, while for those with severe ( $\text{Ca} < 8.0$  mg/dl) and/or symptomatic HYC, a combination of IV and oral supplementation was used. All procedures were performed by three surgeons with similar years of practice and experience in dealing with comparable volumes.

Statistical analysis was performed with STATA v.13 software. Paired Student's t-test was calculated for changes in Ca levels over time and linear mixed models for Ca in different subgroups. The chi-square test of independence was used to evaluate the correlations between various

characteristics of subgroups. A *p* value less than 0.05 was considered statistically significant.

## Results

During the aforementioned period, 122 patients underwent total thyroidectomy at our institution. Three subjects did not agree to participate in the study. Two were excluded because of concomitant pathologies (medullary carcinoma of the thyroid and sarcoidosis), and one patient received calcium oral supplementation before surgery for osteoporosis.

The final number of patients was 116. There were 28 males and 88 females with ages ranging between 16 and 81. The mean age (SD) was 50.1 (14.2) years. Before the surgery, all subjects were normocalcaemic, and the mean calcium levels for all patients were 9.3 (0.4) preoperatively and 8.4 (0.7) postoperatively ( $P < .001$ ). The sample was divided into two groups. Group A included patients for whom parathyroid tissue was found in the specimen (18/116, 15.5%), and group B included all other patients (98/116, 84.5%). For 40 patients (38.8% of the total population), the final diagnosis was cancer (7/18 in group A and 33/98 in group B). In group A, 15 participants (83.3%) had one co-dissected PG, while two had two (11.1%); there were three PGs in only one histopathology report (5.6%). Most of the cancer subgroup had papillary carcinoma, but there were two cases of lymphoma, two cases of Hürthle cell carcinoma and one case of sarcoma.

For lymphoma cases, pre-surgical fine needle aspiration cytology was non-diagnostic (Table 1).

In the immediate postoperative period (two postoperative days), 25 (21.5%) patients developed mild HYC, 34 (29.3%) developed severe and/or symptomatic HYC, and 57 (49.1%) were normal. No statistical significance was observed between groups A and B or between cancer or non-cancer patients (Table 2). Out of the 59 patients that had mild or severe/symptomatic immediate HYC (12 in Group A and 47 in Group B), only 24 developed permanent HYC with no statistical significance between groups (Table 3).

Regarding the incidence of HYP and the need for calcium supplementation, 10.3% were transient, 1.7% were protracted, and 24.1% were permanent after the passage of 3, 6, and 12 months, respectively. Long term medication was needed by 28 patients who developed permanent HYC. Most patients in both groups were normal (61.1% in group A and 64.3% in group B, respectively), followed by permanent (33.3%, 22.4%), transient (5.6%, 11.2%) and protracted (0%, 2%) patients. No statistical significance was demonstrated between groups A and B between cancer and non-cancer patients (Table 4).

The results for patients with cancer were similar to noncancerous patients as cancer was not related to an increased incidence of IP, HYC, or HYP. The results were also similar when cancer patients in the two groups were compared (HYC  $p = .081$ , HYP  $p = .649$ ) (Table 5).

**Table 1: Description of the sample. Group A: patients with incidental parathyroidectomy. Group B: patients with no parathyroid tissue in the histopathology report.**

	Group A	Group B	Total	P value
Total	18 (15.5%)	98 (84.5%)	116	0.16
Male	2 (11.1%)	26 (26.5%)	28 (24.1%)	
Female	16 (88.9%)	72 (73.5%)	88 (75.9%)	
Patients with Cancer	7 (38.9%)	33 (33.7%)	40	0.669

**Table 2: Hypocalcaemia in the immediate postoperative period (two postoperative days). Group A: patients with incidental parathyroidectomy. Group B: patients with no parathyroid tissue in the histopathology report. Normal: Ca levels >8.5 mg/dl, Mild: Ca 8.0 to 8.5 mg/dl, Severe: Ca < 8.0 mg/dl and/or with symptoms of hypocalcaemia.**

	Normal No (%)	Mild No (%)	Severe/symptomatic No (%)	P value
Total	57 (49.1%)	25 (21.5%)	34 (29.3%)	
Group A	6 (33.3%)	3 (16.6%)	9 (50%)	0.109
Group B	51 (52%)	22 (22.4%)	25 (25.5%)	
With cancer	19 (47.5%)	8 (20%)	13 (32.5%)	0.855
No cancer	38 (50%)	17 (22.3%)	21 (27.6%)	

**Table 3: Progression of immediate HYC after 12 months.**

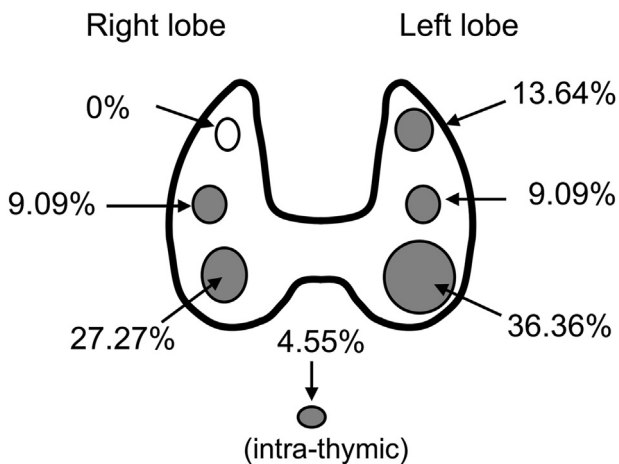
Groups	Permanent No (%)	Protracted No (%)	Transient No (%)	Normal No (%)	P value
Group A					
mild HYC	1 (33.3%)	0 (0%)	0 (0%)	2 (66.6%)	0,66
severe HYC	5 (55.5%)	0 (0%)	1 (11.1%)	3 (33.3%)	
Group B					
mild HYC	6 (27.2%)	1 (4.54%)	5 (22.7%)	10 (45.4%)	0,45
severe HYC	12 (48%)	1 (4%)	5 (20%)	7 (28%)	

**Table 4: Long-term hypoparathyroidism.**

Groups	Normal No (%)	Transient No (%)	Protracted No (%)	Permanent No (%)	P value
Total	74 (63.7%)	12 (10.3%)	2 (1.7%)	28 (24.1%)	
Group A	11 (61.1%)	1 (5.55%)	0 (0%)	6 (33.3%)	0,48
Group B	63 (64.3%)	11 (11.2%)	2 (2%)	22 (22.4%)	
With cancer	22 (55.5%)	3 (7.5%)	2 (5%)	13 (32.5%)	0,08
No cancer	52 (68.4%)	9 (11.8%)	0 (0%)	15 (19.7%)	

**Table 5: Immediate hypocalcaemia and long-term hypoparathyroidism in cancer patients.**

		Patients with cancer		P value
		Group A	Group B	
Long-term HYC	Normal	5	17	0,65
	Transient	0	3	
	Protracted	0	2	
	Permanent	2	11	
Immediate HYC	Normal	3	16	0,08
	Mild	0	8	
	Severe/symptomatic	4	9	

**Figure 1:** Positions and proportions of resected parathyroid glands in relation to the thyroid gland.

Most of the positions of the co-dissected PG in correlation to the thyroid gland were extrathyroidal (10/18, 55.5%), two (11.1%) were intracapsular, and six (33.3%) were intrathyroidal (Figure 1). A total of 77.78% of them were inferior, 22.22% were middle, 16.6% were superior, and one patient (5.6%) was intrathymic.

## Discussion

Conflicting reports exist regarding the correlation between IP and HYP.<sup>16–26</sup> Many authors suggest that a surgeon must try to find and preserve at least three PGs by any means. Among them, Ponce de Leon-Ballesteros et al. stated that appropriate intraoperative PG identification with

in situ preservation of at least three glands might be the most important strategy to prevent transient and permanent postoperative HYC.<sup>16</sup> Compatible with this opinion is Lin YS et al.'s study, according to which IP during thyroidectomy is associated with an increased likelihood of postoperative HYP, and surgeons should perform meticulous dissection to avoid IP and resultant HYC.<sup>27</sup> The majority of relevant studies support the latter, which was also demonstrated by a 2018 meta-analysis performed by Bai et al.<sup>28</sup> The authors conclude that IP increases the risk of postoperative HYC after thyroidectomy; thus, they recommended a more meticulous intraoperative identification of PG to reduce IP, particularly for total thyroidectomy. However, other studies oppose this theory. Baloch et al. found that IP was not associated with an increased incidence of permanent HYP or symptomatic HYC.<sup>21</sup> Chang et al. suggested that identification of PG does not equal safe preservation, as it is not the number of PGs identified but preserved in situ that matters.<sup>17</sup> Lang et al. went even further by implying that identifying fewer PGs in their orthotopic positions not only lowered the risk of temporary and protracted HYP but also shortened the recovery time from protracted HYP.<sup>19</sup>

Our study is more compatible with the second group of authors. It included 116 patients who underwent total thyroidectomy who were divided into two groups: groups A and B with and without IP respectively. Group A included 18 patients (15.5%), which compares well with other published series (8%–23%).<sup>2,7,10–12,14</sup> In most patients' histology reports in group A, only one PG was detected; in two reports, there were two PGs, and in only one report, three PGs were detected. An attempt to separate group A into subgroups according to the number of PGs yielded small subgroups that did not permit further analyses.

It should be emphasized that most of the PGs (68.2%) resected were located in the inferior poles (including the intrathymic region). This could be attributed to the anatomical variations expected in the loci of the inferior PG. They are usually near the inferior poles of the thyroid gland, but they may lie in various positions.<sup>29</sup> In 1–5% of individuals, an inferior parathyroid gland is deep in the superior mediastinum. Interestingly, most incidentally resected PGs (59.1%) were on the left.

In our study, during the immediate postoperative period, most of the patients in group A manifested severe/symptomatic HYC (50%), whereas the majority of individuals in group B were normal (52%). Long-term calcium levels in both groups with mild HYC were normal, in contrast to those with severe/symptomatic HYC, the majority of which eventually developed permanent HYP, with or without IP. Again, no statistical significance was observed between the

incidence of HYP in the groups nor in the correlation between HYP and HYP in each of the groups or for the total population.

There are many reports indicating cancer as a predisposing factor for HYP and HYP.<sup>20,24,30</sup> Sitges-Serra et al. even linked HYP to the size of the tumour, whereas Zheng et al. linked it to delays in diagnosis and treatment.<sup>22,30</sup> Contrastingly, other studies, such as that by Philips et al., failed to associate cancer and HYP.<sup>24</sup> In the present study, there was no statistical significance in the cancer group.

In total, 40 patients had cancer, which corresponded to 38.8% of group A (7/18) and 33.6% (33/98) of group B. Therefore, cancer did not predispose patients to IP. Eight patients with cancer (20%) developed mild HYP, and 13 (32.5%) developed severe HYP. There was no statistical significance when compared to noncancerous patients. All of those with mild HYP belonged to group B, and of those with severe HYP, four belonged to group A (57.1%) and nine to group B (27.2%). Of the cancer subgroup in group A, most of the patients were eventually normal (71.4%), and only 28.5% developed permanent HYP. The same applies for the cancer subgroup in group B, as most patients remained normal (48.4%), followed by permanent (33.3%), protracted (10.1%) and transient (9%) HYP. In general, all the patients with protracted HYP belonged to group B, and they all had cancer. Thus, in the present study, and unlike most published data, cancer was not related to an increased incidence of IP ( $p = .669$ ), HYP ( $p = .855$ ), or HYP ( $p = .08$ ).

This study has obvious limitations. The most significant limitation is that the follow-up was performed via a telephone call, and HYP was defined solely by the need for oral calcium/vitamin D supplementation, as reported by the patients themselves. Most of our patients live far away from the Athens area and visit their family physician or community endocrinologist. Information about the last laboratory findings was not accessible for all patients. Others had not undergone calcium level tests recently and were taking supplements on the advice of their physician. For these reasons, we excluded data pertaining to long-term laboratory confirmation.

## Conclusion

According to our study, incidental parathyroidectomy does not correlate with permanent hypoparathyroidism when at least two parathyroid glands are preserved. Unlike other studies, it was observed that cancer does not increase the incidence of hypocalcaemia or hypoparathyroidism, once again regardless of parathyroid removal. Finally, among our participants, the early presence of severe/symptomatic hypocalcaemia did not predict the eventual presence of permanent hypoparathyroidism.

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## Conflict of interest

The authors have no conflict of interest to declare.

## Ethical approval

This study was approved by the Institutional Review Board and ethics committee of the Office for Human Research Protections Database number IORG0004614. The number of approval is IRB 1418/28-3-16, the ethical approval date is 28/03/2016.

## Authors contributions

TCA conceived and designed the study, conducted research, provided research materials, and collected, organised, and analysed data. TCA and GS interpreted the data, wrote the initial and final drafts of the article, and provided logistical support. PM, IP, TN, AD provided the research materials. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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