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Total Thyroidectomy is Associated with Increased Prevalence of Permanent Hypoparathyroidism

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Background: Thyroid disorders are very common in adults. Despite advances in conservative management, surgery remains a treatment modality of choice in many cases. The mortality and morbidity of thyroidectomy are low, but long-term postoperative hypoparathyroidism (HPT) remains a prominent complication of the procedure.
The aim of this study was to assess the incidence of permanent HPT and identify the risk factors for this complication in a cohort of post-thyroidectomy patients followed at a District Endocrine Clinic.

Material/Methods: This was a retrospective analysis of 401 patients followed up at a Regional/District Endocrine Clinic, who had undergone thyroid surgery in the years 1993–2011. The percentage of patients with permanent (>12 months) HPT was the primary endpoint of the study. The statistically analyzed data of patients with permanent HPT versus the remaining patients free from postoperative complications included their demographic data, indications for surgical treatment of their thyroid disorder, and extent of the thyroid resection. The risk factors for postoperative hypoparathyroidism were assessed using logistic regression analysis.

Results: Permanent HPT following surgery on the thyroid gland occurred in 8.5% of the patients. It was more frequent following total thyroidectomy (20.2%) than near-total thyroidectomy (6.7%) or subtotal thyroidectomy (4.2%); p<0.0001. A multivariate statistical regression analysis demonstrated that primary total thyroidectomy was a significant risk factor for permanent HPT (OR 6.5; 95% CI: 2.9–14.4; p<0.0001).

Conclusions: Total thyroidectomy was associated with increased prevalence of permanent hypoparathyroidism when compared to less extensive thyroid resection modes in patients with benign thyroid diseases.

MeSH Keywords: Hypocalcemia • Hypoparathyroidism • Postoperative Complications • Thyroidectomy

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Background

Thyroid disorders are very common in adults. Despite advances in conservative management, surgery remains a treatment modality of choice in many cases. The mortality and morbidity of thyroidectomy are low, but some long-term post-operative complications are still a significant health and social problem. The present study assessed the rates of permanent hypoparathyroidism (HPT) secondary to thyroid surgery, which is a prominent complication of thyroidectomy.

The aim of this study was to assess the incidence of permanent HPT and identification of the risk factors for this complication based on follow-up of post-thyroidectomy patients in the setting of an outpatient specialist clinic. The rates of permanent HPT were assessed against the demographic profiles of the patients, indications for thyroid surgery, and the extent of the resection of the thyroid gland. The risk factors for hypoparathyroidism were analyzed using the logistic regression method.

Material and Methods

The study was conducted at a District Endocrine Clinic in patients who had undergone surgical treatment for thyroid disorders such as nontoxic multinodular goiter, hyperthyroidism, including toxic goiter and Graves' disease, and Hashimoto's disease. The patients had been operated on at different surgery departments in Poland and subsequently followed up at the District Endocrine Clinic, where they had been referred from the hospital. Patients with the final postoperative diagnosis of thyroid cancer discovered at histological examination were excluded from the analysis, because in line with the general policy, they are followed up at oncology centers for up to 10 years. For the purposes of the study, any patient who underwent repeat thyroidectomy during the study period was considered a new case. The final retrospective analysis covered 401 thyroidectomy procedures performed in the years 1993–2011. The various types of thyroidectomy included: total thyroidectomy (extracapsular resection of both thyroid lobes leaving no remnant thyroid tissue in the neck); near-total thyroidectomy (bilateral resection of both thyroid lobes leaving below 1 ml of remnant thyroid tissue on each side of the neck); hemithyroidectomy (complete removal of 1 thyroid lobe and the isthmus, with retention of the unaffected lobe); and subtotal thyroidectomy (bilateral resection of the thyroid lobes leaving 2–4 ml of the remnant thyroid tissue on each side of the neck). In cases of goiter relapse, reoperative thyroid surgery was performed. The decision about the extent of resection was made by the operating surgeon. The demographic data of the study group, indications for surgery, and types of procedures are presented in Table 1. The diagnosis of permanent HPT was made in patients who required calcium carbonate products and active vitamin D_3 derivatives for longer than 12 months.

Table 1. Demographic and clinical characteristics of patients, type of surgical procedure.

Age; years; mean ±SD (range)	50.79±12.51 (18–80)	
Age; years; n (%)		
18–35	49	(12)
36–64	294	(73)
65–80	58	(15)
Gender; n (%)		
Men	41	(10.2)
Women	360	(89.8)
Indications for surgery; n (%)		
Nontoxic multinodular goiter	243	(60.6)
Toxic multinodular goiter	116	(28.9)
Follicular adenoma	18	(4.5)
Hashimoto's disease	10	(2.5)
Graves' disease	14	(3.5)
Thyroid volume assessed by ultrasonography; ml; median; mean ±SD (range)	49; 63.4±57.2 (7.2–460)	
Hyperthyroidism; n (%)	130	(32.4)
Substernal goiter; n (%)	57	(14.2)
Giant goiter; n (%)	40	(14.1)
Type of surgical procedure; n (%)		
Total thyroidectomy	99	(25)
Near-total thyroidectomy (lobe remnant <1 ml)	30	(7.6)
Subtotal thyroidectomy (lobe remnant 2–4 ml)	238	(60.1)
Hemithyroidectomy	21	(5.3)
Reoperative thyroid surgery	8	(2)

SD – standard deviation.

Statistical analysis.

The quantitative data obtained are presented as arithmetic means plus/minus standard deviation (X±SD), as well as median values. The t-test and its non-parametric equivalent, the Mann-Whitney test, were used to compare the mean quantitative variables between the 2 groups. The F-test (Snedecor) and

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Table 2. Incidence of permanent hypoparathyroidism by demographic and clinical factors.

Factor	Permanent hypoparathyroidism		
	Number or mean ±SD	(%)	P
Age; years	51.12±9.72		0.480
Age; years			
18–35	2	(4.08)	0.340
36–64	29	(9.86)	
65–80	3	(5.17)	
Gender			
Men	1	(2.4)	0.232
Women	33	(9.2)	
Indications for surgery			
Nontoxic multinodular goiter	18	(7.4)	0.389
Toxic multinodular goiter	14	(12.1)	
Follicular adenoma	2	(11.1)	
Hashimoto's disease	0	(0)	
Graves' disease	0	(0)	
Thyroid volume assessed by ultrasonography; ml	63.04±41.98		0.480
Hyperthyroidism	15	(11.5)	0.131
Substernal goiter	4	(10)	0.606
Giant goiter	6	(10.5)	0.759
Type of surgical procedure			
Total thyroidectomy	20	(20.2)	<0.00001
Near-total thyroidectomy	2	(6.7)	
Subtotal thyroidectomy	10	(4.2)	
Hemithyroidectomy	0	(0)	
Reoperative thyroid surgery	2	(25)	

SD – standard deviation.

Tukey's multiple comparison test were used to compare the means of more than 2 groups. In cases of failure to meet the assumptions of variance analysis, the nonparametric Kruskal-Wallis test was used. The chi-square test was employed to determine the relationship between the qualitative characteristics (nonmeasurable variables) and the Fisher exact test when the expected sample size was less than 5. The assessment of potential risk factors for postoperative complications was by the logistic regression analysis. The odds ratio (OR) was determined for each risk factor. STATISTICA, SAS 9.3, and StatCrunch software was used for the calculations. The statistical significance level (P) was 0.05 or lower.

Results

Permanent HPT was identified in 8.5% (34/401) of the study patients. Factors that may affect the occurrence of permanent HPT (patient age and sex, size and location of the goiter, type of thyroid disorder, and the extent of resection) are presented in Table 2. The mean age of patients with normal parathyroid function was 50.3±12.86 years. The mean volume of the thyroid gland assessed by ultrasonography in patients with normal parathyroid function was 61.7±50.3 ml (median, 48.6 ml). There were no statistically significant differences between patients with normal parathyroid function and those

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Table 3. Multivariate logistic regression analysis for hypoparathyroidism.

Parmanent hypoparathyroidism			
Independent factor	**OR**	**95% CI**	**P**
Age	0.98	0.9–1.1	0.251
Female sex*	5.07	0.6–42.9	0.136
Retrosternal goiter	2.26	0.7–6.9	0.154
Hyperthyroidism	1.47	0.7–3.3	0.345
Total thyroidectomy**	6.5	2.9–14.4	<0.0001

* Versus male sex; ** versus near-total thyroidectomy + subtotal thyroidectomy + hemithyroidectomy. OR – odds ratio; CI – confidence interval.

with hypoparathyroidism with regard to the demographic profiles and original thyroid disorder (Table 2). However, there were statistically highly significant differences in the rates of hypoparathyroidism related to the type of thyroidectomy performed (Table 2). Statistically, permanent HPT was the most common after a repeat procedure (25%), but the redo thyroidectomy group was very small (8 patients). On the other hand, for obvious reasons, this complication did not occur after any resection of 1 thyroid lobe with the isthmus. Comparison of the permanent HPT rates with regard to the extent of thyroid resection revealed that total thyroidectomy was especially associated with postoperative permanent HPT (20.2%). The overall permanent HPT rate in all patients who had undergone any kind of primary thyroid surgery was 4.1% (12 patients). Fisher's exact test demonstrated a statistically significant relationship between primary total thyroid resection and permanent HPT occurrence (Table 2).

The multivariate logistic regression analysis was used to assess potential risk factors for postoperative hypoparathyroidism, such as age, female sex, total thyroidectomy, autoimmune thyroid disease, and hyperthyroidism. Table 3 presents findings for a full model including all potential risk factors. The logistic regression analysis revealed that total thyroidectomy was a significant risk factor for permanent HPT (OR 6.5; 95% CI: 2.9–14.4; p<0.0001).

Discussion

Historically, cases of tetany following goiter surgery were first reported in the 1880s by the Swiss surgeon Emil Theodor Kocher, who associated its occurrence with the wound infection [1]. It was only in 1891 that the French physiologist Marcel Gley demonstrated the association between removal of the parathyroid glands and occurrence of tetany [2]. Nowadays, most authors agree that hypocalcemia as a result of either absent or very low secretion of parathormone (PTH) by the parathyroids is associated with inadequate vascular supply of the parathyroid remnants, and only rarely is it due to the accidental removal or damage to all parathyroid glands during thyroidectomy [3–5]. Thus, to avoid permanent hypoparathyroidism, it is recommended to identify as many parathyroid glands as possible and to be meticulous during surgical dissection in order to preserve them *in situ* with an intact vascular supply. However, in cases of inadvertent removal or devascularization of parathyroid glands, all surgeons agree that immediate parathyroid autotransplantation into the sternocleido-mastoid muscle should be used to prevent permanent hypoparathyroidism. Intraoperative iPTH assay can be used to guide the surgeon if parathyroid tissue autotransplantation should be done [6]. According to published studies, inadvertent removal of 1 or 2 parathyroid glands during surgery does not result in postoperative hypocalcemia [7]. Hypocalcemia following surgery may be either completely asymptomatic or present with varying features of neuromuscular irritability, such as tetany and equivalent disorders. Patients usually complain of numbness around the mouth (circumoral paresthesia), or muscle cramps and twitching, and a tingling sensation in the hands [8,9]. Acute hypocalcemia may be manifested by life-threatening cardiovascular events, including a form of ventricular tachycardia known as torsade de pointes, heart blocks, hypocalcemic cardiomyopathy, and heart failure [8,9]. Postoperative parathyroidism requires regular endocrine monitoring and care. It may be successfully treated, although appropriate therapy is sometimes difficult. The clinical features of the disorder include calcification of the basal ganglia, leading to neurological and psychiatric disorders such as extrapyramidal syndromes, Parkinsonism, depression, neuroses, and psychoses. Other characteristic signs (e.g., dry skin, brittle hair and nails, or subcapsular cataract) are trophic changes of tissues derived from ectoderm [8,9].

Treatment of acute severe hypocalcemia after thyroidectomy consists of intravenous administration of calcium carbonate, active metabolites of vitamin D, and in some cases thiazide

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diuretics and phosphate-binders such as aluminum phosphate and aluminum carbonate [8,9]. Serum calcium and phosphorus concentrations are measured regularly and patients must be monitored for calciuria to prevent the symptoms and effects of hypocalcemia and the complications of the treatment, which may include hypercalcemic crisis and renal stones [8]. Usually, up to 12 months after thyroidectomy, normal parathyroid function is recovered and normocalcemia and calcium supplementation may be discontinued [1,3,10]. In the opinion of some authors, recovery of parathyroid function, even when there is postoperative tetany, is possible as late as over 2 years after thyroid surgery. PTH levels normalize and treatment for hypoparathyroidism may be stopped [10,11].

According to the literature, the risk of permanent hypothyroidism is up to 17.3% following thyroid surgery for carcinoma [12]. Compared to the literature data, the overall permanent HPT rate in the present study, which excluded malignant thyroid disease, was high, at 8.5%. Our analysis focused on the effects of risk factors for the development of thyroidectomy complications described in the literature. These factors include female sex and elderly age, a large and substernal goiter, autoimmune thyroid disease and hyperthyroidism, and the extent of thyroidectomy. Although the predominant opinion is that older age (over 65 years) is not a risk factor for postoperative complications, thyroidectomy in the elderly is usually undertaken in cases of cytological diagnosis, suspicion of a malignant thyroid lesion, or the presence of a goiter producing compression symptoms [13–16]. In this study, we found no significant association between older age and permanent HPT, although Thomusch et al., in their analysis of 7266 patients who had undergone benign goiter surgery, found that age was a significant risk factor for this complication [17]. The relationship between patient sex and postoperative hypoparathyroidism is a subject of much controversy. The present study and many other published studies did not confirm any correlation between patient sex and permanent HPT [18]. However, large multicenter analyses from Greece and Germany demonstrated that the risk of permanent hypoparathyroidism was 1.5- to 2.4-fold greater in females [17,19].

Many published studies suggest that the incidence of permanent HPT as a postoperative complication is significantly affected by the original thyroid disease [7,17–21]. Many authors indicate that Graves' disease is an independent risk factor for postoperative hypoparathyroidism [7,17,19,22]. Thus, Witte et al. found a high rate of permanent HPT (5.3%) in patients with the diagnosis of Graves' disease [23]. In the study by Yip et al., 4% of permanent HPT cases were reported after thyroidectomy for Graves' disease [24], which is why patients with Graves' disease are only rarely referred for thyroid surgery. Similarly, in the present study they accounted for just 3.5% of all patients, but there were no cases of permanent HPT in this subgroup. There are some literature reports that claim thyroid surgery does not carry a high risk of complications in Graves' disease, including patients with high titers of the anti-TSH receptor antibodies [25]. Hallgrimsson et al. found that the differences in the incidence of hypocalcemia following total thyroidectomy for Graves' disease and for nontoxic multinodular goiter were not statistically significant [21]. In the opinion of most surgeons, Hashimoto's disease is associated with an increased risk for postoperative complications [26]. In our study, no cases of permanent HPT were found in patients with a history of Hashimoto's disease. This is in agreement with observations of Wormer et al., who did not find permanent HTP in any of the patients operated on for Hashimoto's goiter [27].

In the present study we did not observe any association between the volume and position of the thyroid and the occurrence permanent HTP, which is consistent with the findings reported by some authors [22,28], but others noted a positive correlation between the size of the goiter and its retrosternal location and the occurrence of permanent HTP [29,30]. The optimal extent of thyroid surgery has been long debated by teams of endocrinologists and surgeons. The operation should be radical to achieve good disease control, but minimizing potential post-thyroidectomy complications is equally important [31]. Several types of surgery are employed in the treatment of benign thyroid disease, including total resection of 1 lobe of the thyroid with the isthmus, subtotal removal of both lobes, as well as total or near-total resection of the thyroid gland. An unquestionable advantage of a wide extent of thyroid resection is a lower rate of multinodular goiter recurrence compared to subtotal thyroidectomy [28]. Additionally, following complete excision of the thyroid gland compared to subtotal thyroidectomy, radical reoperative surgery is less frequently required when carcinoma is diagnosed at postoperative histological examination of thyroid tissue surgically removed for indications other than carcinoma [32,33]. Prompt cure of hyperthyroidism, without a further risk of goiter and hyperthyreosis relapse, is another advantage of total and near-total thyroidectomy.

Opinions concerning the frequency of complications following less or more extensive surgery on the thyroid gland cited in the literature differ. In large multicenter studies, a wide resection of the thyroid gland proved to be an independent risk factor for permanent HPT [7,17,19]. In the present study, primary total thyroidectomy was found to produce a significant 6.5-fold increase in the risk for PHTP. Some authors, however, did not observe significantly increased permanent HPT rates after total thyroidectomy compared to subtotal thyroidectomy, both performed for benign thyroid disease [21,22,34–38]. In the study by Songun et al., permanent HTP was observed in 5.2% of the patients and there were no significant differences in its occurrence following either subtotal or total resection of the 2 thyroid lobes [39]. Also, Vaiman et al., in their review of

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7123 patients, did not find any statistically significant differences in the rates of permanent HPT after total thyroidectomy, subtotal thyroidectomy, and hemithyroidectomy, which were 3.5%, 2.5%, and 0.9%, respectively [40]. On the other hand, according to numerous published reports, goiter recurrence and radical reoperative surgery for thyroid carcinoma are associated with higher rates of parathyroid gland insufficiency compared to primary strumectomy [7,17,19,22,28]. Lefevre et al., in a retrospective analysis of 685 strumectomies, found permanent HPT in 2.5% of the patients [41]. Pappalardo et al. reported a high permanent HPT rate in a study of 141 patients. Out of 9 patients who had undergone reoperative surgery for goiter recurrence, 1 was diagnosed with permanent HPT (11%) [42]. In the present study, the rate was even higher, at 25% (2/8 patients), although it should be emphasized that both groups were very small.

Conclusions

Total thyroidectomy is associated with increased prevalence of permanent hypoparathyroidism when compared to less extensive thyroid resection modes in patients with benign thyroid diseases.

Conflict of interest

None.

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