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RESEARCH **ORIGINAL ARTICLE**

Persistent Hypoparathyroidism Following Thyroidectomy: Analysis of 276 Patients

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ABSTRACT

AIM - The aim of this study is to investigate the etiopathogenesis in cases of permanent hypoparathyroidism (PHP) after thyroidectomy.

METHOD - 276 cases diagnosed with permanent hypoparathyroidism (PHP) after thyroid surgery were evaluated retrospectively.

RESULTS - 276 patients who developed post-thyroidectomy PHP were included in this study. 98% had a total thyroidectomy and 70% had no lymph node dissection. In 85% of the patients, PHP developed after their first operation. 63% of the patients had benign disease. No parathyroid glands were found on the final pathology report in 68% of the cases. The operations were performed at university hospitals in 20% of patients. Central lymph node dissections (CLND) were conducted on 27% of patients. 59% of CLND procedures were performed by surgeons under 5 years of experience.

CONCLUSION - The onset of PHP after bilateral thyroidectomy is influenced by many factors. Our study observed a trend linking the likelihood of developing PHP to the surgeon's specialization, experience, the extent of surgery, operations performed in non-academic hospitals, and the conduct of CLND. Notably, even when performed by experienced surgeons, CLND might elevate the risk of this complication. This trend emphasizing surgeon specialization and experience could play an instrumental role in reducing the incidence of this multifaceted complication and underscores the need for greater awareness about the implications of PHP.

KEYWORDS - Parathyroid, hypoparathyroidism, permanent, thyroidectomy, post-thyroidectomy, surgeon experience, risk factors.

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List of Abbreviations:
PHP: Permanent hypoparathyroidism.
CLND: Central lymph node dissection.

INTRODUCTION

Thyroidectomy is the most common endocrine operation in the world. Thyroidectomy is a major surgery performed to treat benign and malignant thyroid diseases. It is associated with three major complications: hypoparathyroidism, recurrent laryngeal nerve injury, and bleeding [1]. There are two types of hypoparathyroidism: transient and permanent [2].

Permanent hypoparathyroidism (PHP) is defined as symptomatic hypocalcemia requiring calcium and vitamin D supplementation after six months from the index procedure [3]. It may develop due to ischemic parathyroid gland damage or accidental removal [3].

Patients have symptoms of hypocalcemia, like paresthesia, muscle cramps, and seizures. They often require hospitalization to control these symptoms in addition to taking calcium and vitamin D drugs life-long, resulting in increased cost and decreased quality of life for patients. In the long term, PHP leads to chronic renal, bone, and cardiovascular diseases and increases the risk of death [4]. The incidence of PHP after thyroid surgery is around 0-3%, although some studies have reported figures as high as 14.5% [5,6]. Multiple studies have examined the risk factors associated with PHP with varying results. Autoimmune diseases, retro-sternal large-volume specimens, malignancy, central lymph node dissection, surgeon experience, and malabsorptive conditions are considered risk factors for developing PHP [5].

Many applications from post-thyroidectomy PHP patients are received by our nationally accredited parathyroid transplantation center at Yeditepe University. This study aims to retrospectively evaluate these patients according to the risk factors of PHP.

METHODS

This is a retrospective, case series descriptive study. The study was approved by the local clinical ethics committee. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects and with the Helsinki Declaration. Consent forms were not required as the data was reported as aggregate numbers and percentages and contained no personal identifiers. Among 310 patients diagnosed with PHP who applied to Yeditepe University Parathyroid Transplantation Center, 276 patients, 211 women and 65 men who developed post-thyroidectomy PHP were included in this study. The age range was 12-67 years, and the mean age among our study sample was 43.6 years. Inclusion criteria of this study included patients who had symptomatic PHP after at least one thyroid surgery, at least 6 months have passed after the surgery, had low levels of serum calcium and PTH, and patients who were required to take oral or parenteral calcium or vitamin D drugs every day regularly. Exclusion criteria of this study included patients who did not have thyroid surgery, had PHP symptoms before surgery, less than 6 months had passed since thyroid surgery, were asymptomatic despite having a low level of serum calcium and PTH, and were not required to take oral or parenteral calcium or vitamin D drugs regularly.

Patients were evaluated retrospectively with regards to the following domains: lymph node dissection, presence of parathyroid glands in the final pathology report, the extent of surgery, the title of the surgeon (endocrine surgeon or not), number of thyroid operations, and experience of the surgeon (≥ Five years or < Five years). Data is presented as numbers and percentages and is analyzed using descriptive statistics.

RESULTS

Total thyroidectomy was performed in 271 patients (98.2%); four patients (1.5%) underwent subtotal thyroidectomy, and one patient had lobectomy. The operation was done for benign causes in 173 patients (62.7%) and for malignant causes in 103 patients (37.3%). Lymph node dissection wasn't performed in 193 (70%) patients, 75 (27%) patients underwent central lymph node dissection, five (1.8%) patients underwent central with unilateral lateral lymph node dissection, and 3 (1.2%) patients underwent central with bilateral lateral neck dissection. Operations were performed by an endocrine surgeon in 37 (13.5%) patients, while 165 (59.7%) patients were operated by non-endocrine surgeons (general surgeon or otolaryngologist), and 74 (26.8%) patients' surgeon specialty is unknown.

The procedures were performed by surgeons with experience of less than five years in 144 patients (52.2%) and by surgeons with experience of more than five years in 66 patients (23.9%).

In the final pathology report, parathyroid glands were not identified in 188 cases (68.1%), one gland was identified in 53 cases (19.2%), two glands in 28 cases (10.2%), and more than two glands were identified in seven cases (2.5%).

PHP developed after the first operation in 235 (85.2%) patients, after the second operation in 34 (12.3%) patients, and after more than two

operations in seven (2.5%) patients.

Thyroidectomy operations were performed in public hospitals for 125 (45.3%) patients, in private hospitals for 95 (34.4%) patients, and in university hospitals for 56 (20.3%) patients (Table 1).

Table 1. Characteristics of the study sample consisting of 310 patients diagnosed with permanent hypoparathyroidism who applied to Yeditepe University Parathyroid Transplantation Center.

Criteria	n	%
Extent Of Surgery		
Total Thyroidectomy	271	98.2%
Subtotal Thyroidectomy	4	1.5%
Lobectomy	1	0.3%
Pathology		
Benign	173	62.7%
Malignant	103	37.3%
Lymph Node Dissection		
No Dissection Done	193	70%
Only Central lymph node dissection	75	27%
CLND+One Side Lateral neck dissection	5	1.8%
CLND+Two Side Lateral neck dissection	3	1.2%
Endocrine Surgeon Vs Others		
Yes	37	13.5%
No	165	59.7%
Unknown	74	26.8%
Surgeon Experience		
< Five Years	144	52.2%
> Five Years	66	23.9%
Unknown	66	23.9%
Parathyroid Glands on Final Pathology Report		
Not Identified	188	68.1%
One Gland	53	19.2%
Two Glands	28	10.2%
> Two Glands	7	2.5%
Re-Operative Surgery		
First Operation	233	85.1%
Second Operation	34	12.3%
>2 Operations	7	2.5%
Hospital Sector		
Public	125	45.3%
Private	95	34.4%
University	56	20.3%

Of the 75 patients who had central lymph node dissection (CLND), 18 (24%) were performed by an endocrine surgeon, 47 (62.6%) were performed by non-endocrine surgeons (general surgeon or otolaryngologist), and 10 (13.4%) by unknown surgeons. In 44 (58.6%) patients CLND were performed by surgeons with an experience of less than five years; in 14 (18.6%) patients were performed by surgeons with an experience of more than five years; and in 17 (22.8%) patients were performed by the surgeons of unknown experience (Table 2).

Table 2. Central lymph node dissection patients' data according to surgeon specialty and experience.

Central Lymph Node Dissection Performed Surgeons	n	%
Speciality		
Endocrine Surgeon	18	24%
Non-endocrine Surgeon	47	62.6%
Unknown	10	13.4%
Experience		
< Five years	44	58.6%
> Five years	14	18.6%
Unknown	17	22.8%

DISCUSSION

PHP is a serious complication of thyroidectomy [5,6]. It occurs due to intraoperative direct tissue damage to the parathyroid glands, their blood supply, or accidental removal of the glands during the procedure. The incidence of postoperative hypoparathyroidism is inconsistent in the literature, mostly due to the variation in definitions used in different studies. A meta-analysis study by Edafe et al. revealed that the incidence of postoperative transient and permanent hypoparathyroidism was between 19% to 38% and between 0% to 3% [7]. In a retrospective, multi-center, and nationwide study, the incidence of permanent hypoparathyroidism was found to reach 14.5% [6].

PHP makes the patient physically and psychologically devastated and decreases the quality of life. For this reason, it has been a focus of research to identify its incidence and the risk factors associated with its development. In the ATA statement on postoperative hypoparathyroidism published in 2018, bilateral thyroid operations, autoimmune thyroid disease, substernal goiter, low-volume thyroid surgeon, central neck dissection, malabsorptive conditions, and prior central neck surgery were considered risk factors for the development of permanent hypoparathyroidism [5].

Bilateral thyroid surgery is a constant risk for developing permanent hypoparathyroidism, as reported in many studies [8]. Most of our patients had bilateral thyroid surgery, which is consistent with the literature; manipulation on both sides of the thyroid increases the risk of damaging, de-vascularizing, or removing the parathyroid glands, as these glands can sometimes be mis-

taken as lymph nodes or fat tissue.

Thyroid pathology has been studied as a risk factor for developing PHP with inconsistent results. Dedivitis et al. and Canu et al. found that Graves' disease and heavier thyroid specimens are independent risk factors for permanent hypoparathyroidism [9,10]. Imga et al. concluded that malignancy should be considered an independent risk factor for developing PHP [11]. Benign inflammatory thyroid diseases induce adhesions to the surrounding tissues, and the thyroid gland is more vascular with an increasing risk of bleeding, making identifying and preserving parathyroid glands more difficult. On the other hand, malignancy requires more extensive surgery and the addition of lymph node dissection, which puts the parathyroid glands at increased risk of injury [12]. In our study, the occurrence of PHP was noticed in both groups with benign and malignant diseases, with higher numbers in patients with benign diseases. This could be due to higher numbers of operations done for benign causes at that time or because of the presence of other contributing factors like surgeon experience. We also noticed that 81% of patients with malignant disease who developed PHP received lymph node dissection. This finding may suggest that it is not the pathology that matters; it could be the extent of surgery that puts these patients at risk of developing PHP.

There is a consensus on the role of central lymph node dissection (CLND) in patients with clinically positive lymph nodes. However, there is still a debate on the role of prophylactic CLND in managing differentiated thyroid cancers [13,14]. In the prospective randomized clinical study, Viola et al. found that total thyroidectomy and total thyroidectomy with prophylactic CLND had a similar outcome when performed for cN0 patients with papillary thyroid carcinoma [15]. Meanwhile, multiple studies have demonstrated the morbidity of CLND and revealed that this procedure is an independent risk factor for PHP [16]. In our study, 75 (27%) patients had CLND, while 193 (70%) patients did not have dissection. Given the consensus on the morbidity of CLND and the controversy about the role of prophylactic CLND, it is wise to balance the benefits and risks before deciding to proceed with it, and this decision should be made by an expert endocrine surgeon.

Preservation of parathyroid glands during thyroidectomy is of critical importance, and if accidentally removed, it should be auto-transplanted to minimize the risk of permanent hypoparathyroidism [17]. Diez et al. found that the number of parathyroid glands on pathology reports is a risk factor for developing permanent hypoparathyroidism [6]. Most of our patients have no glands identified on the final pathology report (68%), which may indicate that the main mechanism of hypoparathyroidism is our cases, damage or devascularization of the parathyroid glands during thyroidectomy.

It is well established that surgeon experience and the number of operations performed have a positive impact and are associated with lower morbidity. Meltzer et al. revealed that the risk of transient and permanent complications after thyroidectomy is decreased when the surgeon's annual volume increases [18]. These data are consistent with our results, where a substantial portion of patients were operated on by surgeons from various specialties (60%) and those with less than 5 years of experience (52%). The lower number of PHP cases post thyroidectomies operated on by endocrine surgeons can probably be explained by the case volume and the additional fellowship training. It is worth mentioning that the number of patients who have CLND done by an endocrine surgeon is 18 (24%), while the number of patients who were operated on by an endocrine surgeon is 37 (13.5%). This reflects the fact that endocrine surgeons do more neck dissections than other surgeons. This could be the cause of the number of patients who are operated on by endocrine surgeons, as CLND itself may contribute to the development of PHP. The number of patients operated on at university hospitals (20%) is less than in other sectors, mostly due to the availability of experienced endocrine surgeons and more adherence to guidelines in academic settings, which probably creates a positive influence.

It is accepted that re-operative surgery on the thyroid poses an increased risk of complications due to adhesions, scar tissue, and distorted anatomy. Many studies have demonstrated an increased risk of permanent hypoparathyroidism after re-operative surgery [19,20]. On the contrary, others have concluded that re-operative surgery and completion surgeries do not have an increased risk of permanent complications and, when indicated, should be carried out without fear of the increased risk of complications [21]. In our study 85% of cases developed PHP after the first operation. Given the lack of data regarding the overall number of procedures performed, accurate conclusions related to risk after re-operative surgery cannot be drawn from our study. Considering these results, PHP is multifactorial, and working to improve these factors combined would reduce the rate of these complications. We emphasize that thyroidectomy is a major surgical procedure that has a debilitating permanent complication, which leads to decreased quality of life and increased costs; therefore, it should be

performed by an experienced endocrine surgeon. We also encourage adherence to recent guidelines to minimize the extent of surgery and the rate of complications. Large prospective well-designed studies are warranted to better predict the occurrence of PHP and its related risk factors.

AVAILABILITY OF DATA

The data used and/or analyzed during the study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

INFORMED CONSENT

Consent forms were not required as the data was reported as aggregate numbers and percentages and did not contain any personal identifiers.

ETHICS COMMITTEE

The study was approved by the local clinical ethics committee. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration

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