

## Lymphocytic Infiltration of The Thyroid Gland in Relation to The Clinical and Biochemical Parameters in Thyrotoxicosis

Mohamed Mahmoud Ahmed Abdel-Kader<sup>1\*</sup>, Atef Mohamed Abdellatif<sup>1</sup>, Ibrahim El-Dosoky<sup>2</sup>, Mohammad Hossam El-Dein<sup>1</sup>, Ahmed Elsayed Lotfy<sup>1</sup>

<sup>1</sup> Endocrine Surgery Unit, Faculty of Medicine, Mansoura University, Dakahlia, Egypt

<sup>2</sup> Pathology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt

\*Corresponding author: Mohamed Mahmoud Ahmed Abdel-Kader,

Mobile: 01021850661, Email: Moomahmoud1993@gmail.com

### ABSTRACT

**Background:** Thyrotoxicosis is a clinical condition induced by tissue exposure to excess free thyroid hormones, especially thyroxine (T<sub>4</sub>) and/or triiodothyronine (T<sub>3</sub>). **Aim:** This study aimed to determine the relation between the lymphocytic infiltration degree and the postoperative manifestations of either recurrence or hypothyroidism.

**Patients and methods:** This prospective comparative research was performed on one hundred cases of thyrotoxic goiter admitted to Mansoura University Endocrine Surgery Unit from December 2021 to December 2023.

**Results:** The lymphocytic infiltration degree in the removed thyroid specimen was recorded. The majority of our patients were classified as grade 0 in 29 patients (29%), followed by grade 3 in 25 patients (25%), grade 1 in 23 patients (23%) and grade 2 in 23 patients (23%). They were separated into two equal groups. Six patients (12%) in group "A" who underwent total thyroidectomy (TT) showed hypothyroid manifestations, where there was grade 0 and grade 1 lymphocytic infiltration in specimens which can be corrected by giving levothyroxine (Eltroxin™). Four patients (8%) in group "B" who underwent near total thyroidectomy (NTT) showed recurrence of thyrotoxic manifestations where there was grade 2 and grade 3 lymphocytic infiltration in specimens which can be corrected by radioactive Iodine (RAI).

**Conclusion:** Postoperative hypothyroidism was detected in 12 patients with mild lymphocytic infiltration after TT, while recurrence was observed in 8 patients with heavy lymphocytic infiltration after NTT in patients with thyrotoxic goiter.

**Keywords:** Thyrotoxicosis, Thyrotoxic goiter, Lymphocytic infiltration, Total thyroidectomy, Near total thyroidectomy.

### INTRODUCTION

The thyroid is a gland that has a major impact. The mature thyroid gland, which is positioned in the neck, is responsible for transporting hormones throughout the body. Thyroxine and calcitonin are hormones released by the thyroid that affect the basal metabolic rate of the body, brain, heart, digestive tract, muscle, and calcium homeostasis<sup>(1)</sup>. Thyrotoxicosis is the clinical condition caused by tissue exposure to excess circulating free thyroid hormones, thyroxine (T<sub>4</sub>) and/or triiodothyronine (T<sub>3</sub>). It is one of the most popular endocrine clinical presentations, involving about 1–1.5% of the population and occurring five to ten times more frequently in females than males<sup>(2)</sup>.

Untreated or improperly managed thyrotoxicosis leads to an elevated probability of cardiovascular mortality, atrial fibrillation, osteoporosis, thromboembolic problems, neuropsychiatric disorders, and considerable impairment of quality of life<sup>(3)</sup>. Hyperthyroidism was diagnosed when blood thyroid-stimulating hormone (TSH) levels remained consistently subnormal while free thyroid hormone levels were within or above corresponding reference intervals. The main etiologies of thyrotoxicosis contain toxic multinodular goitre (TMG), Graves' disease (GD), thyroiditis, and toxic adenoma (TA). All of which need an appropriate differential diagnosis because each necessitates a different therapeutic approach<sup>(4)</sup>. Total thyroidectomy (TT) with a uniform capsular dissection approach is the recommended method around the world.

Theodore Kocher first introduced total thyroidectomy in 1880, using a typical technique of capsular dissection<sup>(5)</sup>. It was already recognized that the lymphocytic infiltration in the thyroid gland during surgery predicts hypothyroidism<sup>(6)</sup>.

This was a prospective comparative study that aimed to determine the relation between the lymphocytic infiltration degree and the postoperative manifestations of either recurrence or hypothyroidism.

### PATIENTS AND METHODS

This prospective comparative research has been performed on one hundred cases of thyrotoxic goiter who were admitted to Mansoura University Endocrine Surgery Unit for Two-year duration from beginning of December 2021 to the end of December 2023. They were separated arbitrary into 2 equal groups: **Group "A" (Total thyroidectomy group):** Total thyroidectomy has been done for 50 patients (7 patients were primary toxic goiter and the remaining 43 patients were secondary toxic goiter). **Group "B" (Near total thyroidectomy group):** Included 50 patients with secondary thyrotoxicosis who underwent near total thyroidectomy. The lymphocytic infiltration degree of the removed thyroid specimen was recorded according to **Bhatia et al.**<sup>(7)</sup> classification into grade zero (no lymphocytic infiltration), grade one (mild), grade two (moderate) and grade three (severe). Our patients were followed up monthly over 6 months.

**Inclusion criteria:** Patients with thyrotoxicosis.

**Exclusion criteria:** Cases with history of previously thyroid operation, pregnant females, Psychiatric patient and patients with simple multinodular goiter.

**All patients were subjected to the following:**

Full history taking. Clinical examination. Radiological investigations (Thyroid ultrasound, CT scan if huge MNG with retrosternal extension was found. Thyroid scan if needed). Biological investigation including thyroid function tests (TSH, free T<sub>3</sub> & T<sub>4</sub>). Routine laboratory investigations.

- **Indirect laryngoscopy** to check the mobility of vocal cords.
- **ECG.**
- **Post-Operative pathological examination:** of the removed thyroid specimen was done and the degree of lymphocytic infiltration was recorded according to **Bhatia et al.** [7] classification into:  
Grade zero: no lymphocytic infiltration. Grade one: mild. Grade two: moderate. Grade three: severe. Accordingly, we performed postoperative pathological examination of the removed thyroid specimen using paraffin section and light microscope.

**Operative data:** All operations were performed under general anesthesia. In total thyroidectomy both thyroid lobes were removed totally (**Figure 1**). In near total thyroidectomy: Removal of both thyroid lobes leaving small slice in the posteromedial aspect on one side (**Figure 2**).

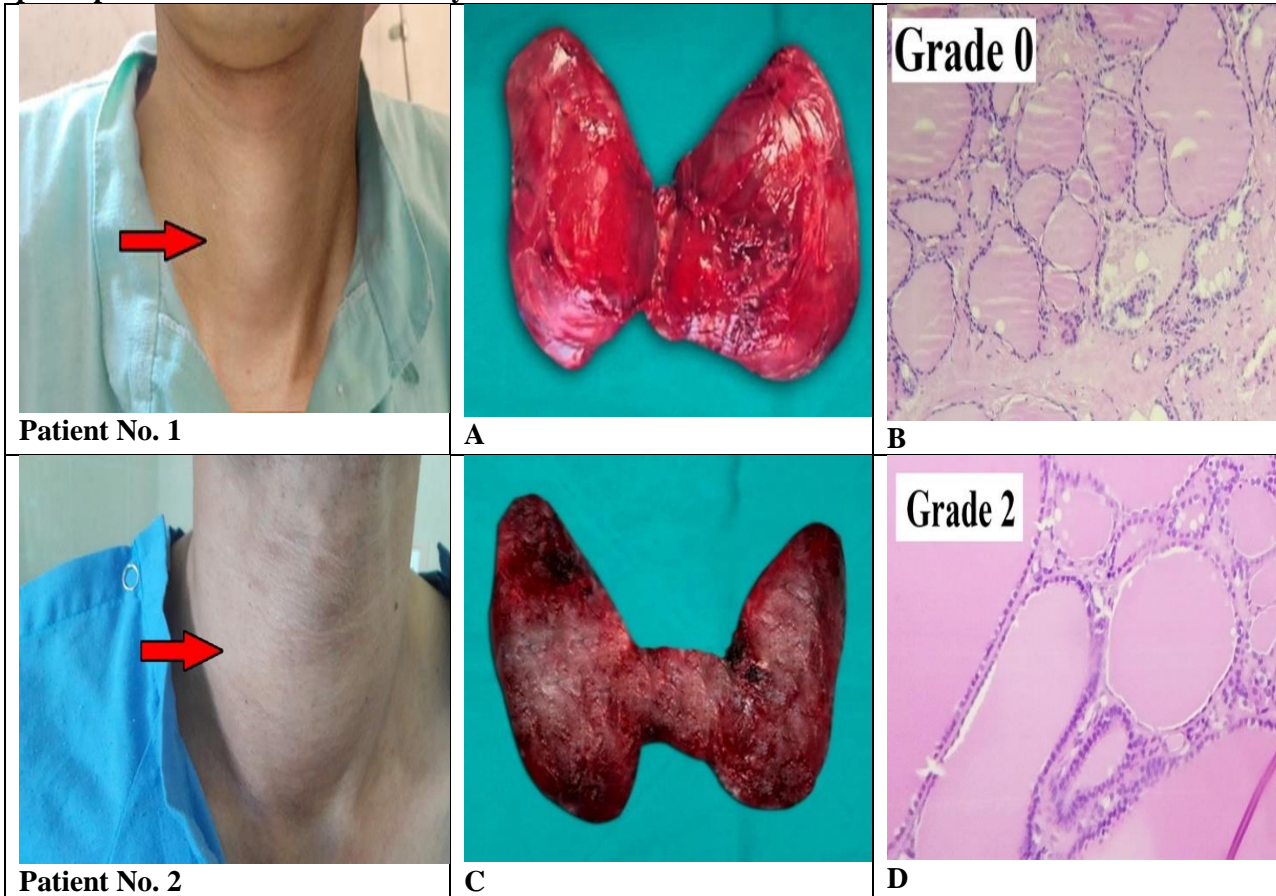
**Postoperative follow-up:** Our patients were followed up three months and six months after operation for postoperative manifestations of either recurrence or hypothyroidism.

**Ethical considerations:** Mansoura University Ethical Committee, Egypt had ethically approved the present research protocol (IRB Code Number: MS.21.12.1797.R1). Every individual involved in the study provided informed consent. Confidentiality and personal privacy were preserved throughout the study. The collected data was not taken for any other purpose. The ethics, morals, culture, and beliefs of the subjects were honored. The Helsinki Declaration was followed throughout the course of the investigation.

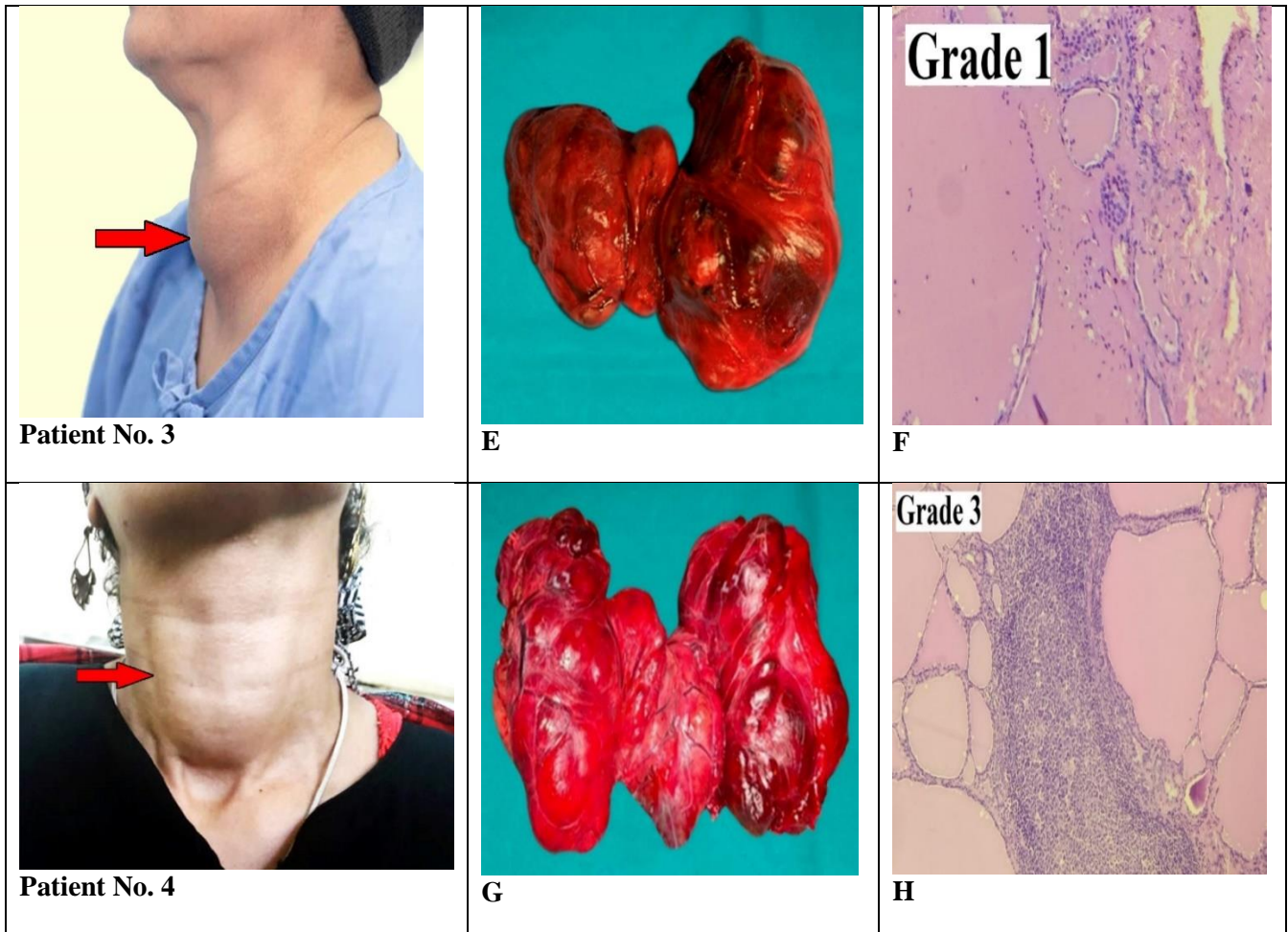
**Data collection:**

The information gathered on a completed sheet were input into an electronic spreadsheet (Microsoft Excel) and analyzed utilizing SPSS (Statistical Package for Social Sciences) version 26 for Windows® (IBM SPSS Inc., Chicago, IL, United States of America). The tests which used in this study were Chi square test and student T test by using SPSS programme.

**Example of patients included in our study:**



**Figure (1): Patient No. 1:** Male patient 39 years old with primary diffuse toxic goiter, who underwent total thyroidectomy (Group A). **A:** Thyroid gland specimen of diffuse toxic goiter of the same patient. **B:** Focused slide of thyroid tissue showing no lymphocytic infiltration (Grade "0" lymphocytic infiltration) of the same patient. **Patient No. 2:** **C:** Thyroid gland specimen of primary toxic goiter of the same patient. **D:** Focused slide of thyroid tissue showing aggregates of lymphoid cells around atrophic acini (Grade "2" lymphocytic infiltration) of the same patient.



**Figure (2): Patient No. 3:** Female patient 43 years old with secondary multinodular toxic goiter, who underwent near total thyroidectomy (Group B). **E:** Thyroid gland specimen of secondary toxic goiter of the same patient. **F:** Focused slide of thyroid tissue showing small clusters of lymphocytic infiltration beside thin-walled vessel (Grade "1" lymphocytic infiltration) of the same patient. **Patient No. 4:** Female patient 62 years old with secondary multinodular toxic goiter who underwent near total thyroidectomy (Group B). **G:** Thyroid gland specimen of secondary toxic goiter of the same patient. **H:** Focused slide of thyroid tissue showing lymphoid aggregate up to lymphoid follicles with germinal centers and surrounding thyroid acini with no Hurthle cell change (Grade "3" lymphocytic infiltration) of the same patient.

## RESULTS

During the period from the beginning of December 2021 to the end of December 2023, 100 patients were used in our study. Seven patients were primary toxic goiter and the remaining were secondary toxic goiter. They were 89 females and 11 patients were males. According to the operation performed, our cases were separated into two main groups. Group "A" (50 cases) had total thyroidectomy and group "B" (50 cases) underwent near total thyroidectomy. A statistically insignificant variance has been observed among groups regarding age, gender, preoperative TSH, smoking, diabetes, CKD, BA, epilepsy, RA, hepatitis, and gastroesophageal reflux disease (GERD), but there was a statistically significant variance according to goiter type and cardiac disease (Table 1).

**Table (1):** Analysis of the demographic and clinical data in the two study groups

		<b>Group (A) Total Thyroidectomy (n = 50)</b>	<b>Group (B) Near total thyroidectomy (n = 50)</b>	<b>P value</b>
<b>Type of goiter</b>	1 <sup>st</sup> toxic goiter	7 (14 %)	0	0.000
	2 <sup>nd</sup> toxic goiter	43 (86%)	50 (100%)	
<b>Gender</b>	Male	6 (12 %)	5 (10%)	1.0
	Female	44 (88%)	45 (90%)	
<b>Age</b>				
Mean ± SD		43.8 ± 10.9	46.18 ± 10.2	0.264
<b>Preoperative TSH</b>				
Mean ± SD		0.078 ± 0.017	0.081 ± 0.016	0.361
<b>Medical History</b>				
<b>DM</b>	Non-Diabetic	46 (92%)	41 (82%)	0.219
	Pre-Diabetic	0	1 (2%)	
	Diabetic	4 (8%)	8 (16%)	
<b>HTN</b>	Yes	9 (18%)	10 (20%)	0.799
	No	41 (82%)	40 (80%)	
<b>Cardiac</b>	Yes	10 (20%)	3 (6%)	0.033
	No	40 (80%)	47 (94%)	
<b>CKD</b>	Yes	1 (2%)	0	0.237
	No	49 (98%)	50 (100%)	
<b>BA</b>	Yes	1 (2%)	1 (2%)	1
	No	49 (98%)	49 (98%)	
<b>Epilepsy</b>	Yes	2 (4%)	0	0.093
	No	48 (96%)	50 (100%)	
<b>RA</b>	Yes	1 (2%)	0	0.237
	No	49 (98%)	50 (100%)	
<b>Hepatitis</b>	Yes (HCV)	6 (12%)	6 (12%)	1
	No	44 (88%)	44 (88%)	
<b>GERD</b>	Yes	1 (2%)	1 (2%)	1
	No	49 (98%)	49 (98%)	
<b>Personal habits</b>				
<b>Smoking</b>	Yes	4 (8%)	4 (8%)	1
	No	46 (92%)	46 (92%)	

Table (2) showed a comparison of the distribution of grades of lymphocytic infiltration in relation to total thyroidectomy and near total thyroidectomy, along with their respective p-values. The p-value for the comparison of grades was 0.000 for Grade 0, and the  $X^2$  value was 64.670, which was statistically significant.

**Table (2):** Relation between lymphocytic infiltration and type of operation

	<b>Total Thyroidectomy</b>	<b>Near total thyroidectomy</b>	<b>X<sup>2</sup></b>	<b>P value</b>
<b>Grade 0</b>	2 (4%)	27 (54%)	64.670	0.000
<b>Grade 1</b>	4 (8%)	19 (38%)		
<b>Grade 2</b>	21 (42%)	2 (4%)		
<b>Grade 3</b>	23 (46%)	2 (4%)		

Our patients were followed up three months and six months after operation. **After 3 months of follow up:** In group A, patients where total thyroidectomy was done, hypothyroidism was detected in six patients where there was no and/or mild lymphocytic infiltration (Grade 0 and Grade 1). These patients received levothyroxine to correct the hypothyroidism detected. The remaining 44 patients showed moderate and/or severe lymphocytic infiltration (Grade 2 and Grade 3) with no recurrence and no manifestations of hypothyroidism (Table 3).

**Table (3):** Percentage of hypothyroidism in group A after follow up for 3 months postoperative

	Hypothyroidism	No Hypothyroidism	Mean ± SD	P valve	95 % CI
N	6	44	1.88 ± 0.328	0.384	1.787 – 1.973
Percentage	12%	88%			

Table (4) compared the hypothyroidism rates between total thyroidectomy and near total thyroidectomy. There was significant difference between type of operation and hypothyroidism (O.R = 0.880, 95% CI = 0.794 – 0.975 & P = 0.012).

**Table (4):** Relation between hypothyroidism and type of operation.

Hypothyroidism	Total thyroidectomy	Near total thyroidectomy	X'	P valve	O.R	95 % CI
Yes	6 (12%)	0	6.383	0.012	0.880	0.794 – 0.975
No	44 (88%)	50 (100%)				

In group B, patients where near total thyroidectomy was done, recurrence of the thyrotoxic manifestations was detected in four patients where there was moderate and/or severe lymphocytic infiltration (Grade 2 and Grade 3). They were referred to the Oncology and Nuclear Medicine Department for completion of thyroidectomy with radioactive Iodine (RAI). The remaining 46 patients showed no recurrence of the thyrotoxic manifestations (Table 5).

**Table (5):** Percentage of recurrence of manifestations in group B after follow up for 3 months postoperatively

	Recurrence	No recurrence	Mean ± SD	P valve	95 % CI
N	4	46	1.92 ± 0.274	0.000	1.842 – 1.998
Percentage	8%	92%			

Table (6) compared the recurrence rates between total thyroidectomy and near total thyroidectomy. A significant distinction has been observed among type of operation and recurrence (O.R = 1.087, 95% CI = 1.002 – 1.180 & P = 0.041). These data implied that total thyroidectomy might offer a significant advantage in terms of reducing the risk of recurrence compared to near-total thyroidectomy (Table 6).

**Table (6):** Relation between recurrence and type of operation

Recurrence	Total thyroidectomy	Near total thyroidectomy	X'	P valve	O.R	95 % CI
Yes	0	4 (8%)	4.167	0.041	1.087	1.002 – 1.180
No	50 (100%)	46 (92%)				

At 6 months, patients with hypothyroid manifestations responded well to medical therapy in the form of levothyroxine (Eltroxin™), while patients with recurrent manifestations responded well to medical therapy in the form of radioactive Iodine (RAI). Many studies were focused on the lymphocytic infiltration grading and its relation with the serologic parameters and we made a comparison between present study and previous studies as shown in table (7).

**Table 7:** Comparison between previous studies and present study.

Study	Number of patients	Duration of study (years)	Sex		Grade of lymphocytic infiltration (%)				Hormonal status (%)			
			Male	Female	Grade 0	Grade 1	Grade 2	Grade 3	Euthyroid	Hypothyroid	Hyperthyroid	
Previous	Bhatia <i>et al.</i> <sup>[7]</sup>	76	3	6	70	-	38.6	44	17.3	0	98.6	1.3
	Anila <i>et al.</i> <sup>[12]</sup>	60	1.5	5	55	-	45	36.6	18.3	65	30	5
	Saraf <i>et al.</i> <sup>[10]</sup>	134	4	8	128	-	42.5	52.2	5.2	23.6	60.6	15.7
	Kudva and Kishore <sup>[13]</sup>	50	0.5	3	47	-	58	28	14	28	64	8
	Thomas <i>et al.</i> <sup>[14]</sup>	144	10.5	15	129	-	-	-	-	31.9	44.4	20.8
	Sharma <i>et al.</i> <sup>[11]</sup>	52	1	6	46	-	15.4	80.8	3.8	34.6	30.8	34.6
Present study	100	2	11	89	29	23	23	25	0	0	100	

## DISCUSSION

The demographic findings of this study revealed that most cases were females, resulting in a male to female ratio of about 11:89, with a mean age of  $45.0 \pm 10.5$  years. This is in agreement with **Abdel-Latif et al.**<sup>(8)</sup> who noted that males represented twelve cases (14%) while females represented seventy two cases (86%) with a mean age of  $41.43 \pm 9.27$  years. Both studies highlighted a predominance of female patients, although the average ages vary slightly, indicating differences in the populations examined. Another comparative study by **Divya and Damodaran**<sup>(9)</sup> revealed that most of the cases in their research were females, with female: male ratio of 32:1.

**Saraf et al.**<sup>(10)</sup> stated that the disparity is caused by female sex steroid hormones and the X chromosome, which contains several sex and immune-related genes.

100 patients were used in our study. Seven patients (7%) were primary diffuse toxic goiter and the remaining 93 patients (93%) were secondary multinodular toxic goiter. In **Divya and Damodaran**<sup>(9)</sup> study, most of the patients presented with diffuse thyroid enlargement (88.0%), multinodular enlargement & solitary nodule have been encountered in 8.7% and 3.3% of the cases respectively.

The mean preoperative TSH concentration of patients underwent total thyroidectomy was  $0.078 \pm 0.017$ , while the mean preoperative TSH concentration of cases of near total thyroidectomy was  $0.081 \pm 0.016$ . **Abdel-Latif et al.**<sup>(8)</sup> reported that the mean pre-operative TSH concentration was  $0.11 \pm 0.07$  in total thyroidectomy group and  $0.12 \pm 0.08$  in near total thyroidectomy group.

Post-operative pathological examination of the removed thyroid specimen was done and the degree of lymphocytic infiltration was recorded. The majority of our patients were classified as grade 0 in 29 patients (29%), followed by grade 3 in 25 patients (25%), grade 1 in 23 patients (23%) and grade 2 in 23 patients (23%). **Sharma et al.**<sup>(11)</sup> noted that grade II thyroiditis was the most frequent finding and was seen in 42 (80.8%) of cases followed by grade I in 8 (15.4%) and grade III in 2 (3.8%). **Divya and Damodaran**<sup>(9)</sup> found that lymphocytic infiltration was subclassified as grade 0 (no infiltration), grade one (mild), grade two (moderate) and grade three (severe) in 20.0%, 64.0% and 16.0% of the cases respectively as per criteria devised by **Bhatia et al.**<sup>(7)</sup>.

In present study, we found statistically significance in distribution of grades of lymphocytic infiltration in relation to total thyroidectomy and near total thyroidectomy ( $P = 0.000$ ). Grade 0 was detected in two patients (4%) who underwent total thyroidectomy, while it was detected in 27 patients (54%) who underwent near total thyroidectomy. Grade 1 was detected in four patients (8%) who underwent total thyroidectomy, while it was detected in 19 patients (38%) who underwent near total thyroidectomy. Grade 2 was detected in 21 patients (42%) who underwent total

thyroidectomy, while it was detected in two patients (4%) who underwent near total thyroidectomy. Grade 3 was detected in 23 patients (46%) who underwent total thyroidectomy, while it was detected in two patients (4%) who underwent near total thyroidectomy.

Our patients were followed up for three months and six months after the operation. In our research, we found a significant relation among type of operation and hypothyroidism ( $P = 0.012$ ). Six patients (12%) in group "A" who underwent total thyroidectomy showed hypothyroid manifestations where there was grade 0 and grade 1 lymphocytic infiltration in the removed thyroid specimens which can be corrected by giving levothyroxine (Eltroxin™).

**Chotigavanich et al.**<sup>(6)</sup> noted that the degree of lymphocytic infiltration in the thyroid, assessed during surgery, might predict post-surgical hypothyroidism

Regarding the recurrence of thyrotoxic manifestations, the current study revealed that there was a significant relation among type of operation and recurrence ( $P = 0.041$ ). Four patients (8%) in group B who underwent near total thyroidectomy showed recurrence of thyrotoxic manifestations where there was grade 2 and grade 3 lymphocytic infiltration in the removed thyroid specimens, which can be corrected by radioactive iodine (RAI). In contrast, **Abdel-Latif et al.**<sup>(8)</sup> noted that after six months the monitoring, TSH concentrations exhibited dropped levels in two cases (4.8%) in the near total thyroidectomy (NTT) group and the toxic manifestations began to be presented on cases. **Franklyn and Boelaert**<sup>(15)</sup> pointed out that radioiodine (RAI) was an effective treatment, which had been used for over 75 years in the treatment of Graves' thyrotoxicosis.

Our study proved that total thyroidectomy is the best operation to be done in patients with thyrotoxicosis. It was shown that there was no recurrence detected in all patients where total thyroidectomy was done whatever the degree of lymphocytic infiltration in the removed thyroid specimen. According to **England and Atkin**<sup>(16)</sup>, total thyroidectomy was the only suitable surgical treatment for thyrotoxicosis in the United Kingdom.

## CONCLUSION

No recurrence detected in all patients with thyrotoxic goiter where total thyroidectomy was done whatever the degree of lymphocytic infiltration in the removed thyroid specimen. In patients with thyrotoxic goiter where total thyroidectomy was performed, postoperative hypothyroidism was detected in six patients (12%) where there was mild lymphocytic infiltration (Grade 0 & grade 1) in the removed thyroid specimens. This was corrected by giving levothyroxine (Eltroxin™). In patients with thyrotoxic goiter where near total thyroidectomy was performed, postoperative recurrence of manifestations was detected in four patients (8%) where there was heavy lymphocytic infiltration (Grade 2 & grade 3) in the removed thyroid

specimens. This was corrected by postoperative radioactive iodine (RAI) for ablation. Total thyroidectomy is the best operation to be done in patients with thyrotoxic goiter.

#### DECLARATIONS

- **Consent for publication:** I certify that each author has granted permission for the work to be submitted.
- **Funding:** No fund                      **Availability of data and material:** Available
- **Conflicts of interest:** No conflicts of interest.
- **Competing interests:** None.

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