

## Original Research Article

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# Histopathological pattern of thyroid diseases and its correlation with post-thyroidectomy hypocalcemia: a prospective study in iodine-sufficient Southern India

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## ABSTRACT

**Background:** Increasing incidence of thyroid diseases requiring surgery and postoperative hypocalcemia after total thyroidectomy (TT) remains a concern. This prospective study evaluated the correlation between the histopathologic pattern of thyroid disease and the development of temporary and permanent hypocalcemia (>6 month) post-TT.

**Methods:** Demographics and clinical profile of consecutive patients undergoing TT were documented. The final diagnosis was confirmed with histopathological examination (HPE) of thyroidectomy specimen. Serum corrected-calcium and intact parathormone was measured at baseline, 48-hour and 6-month post-TT.

**Results:** Out of 328 subjects (mean age=35.5 year; M:F=65:263), 33.4% (n=109) and 7.6% (n=26) developed temporary and permanent hypocalcemia [calcium=8 mg/dl] post-TT. HPE comprised colloid goitre 33.2% (n=109), follicular adenoma 1.8% (n=6), Hashimoto's/lymphocytic thyroiditis 16.8% (n=55), Graves' disease 14% (n=46), adenomatous hyperplasia 19.8% (n=65), papillary thyroid carcinoma (PTC) 13.4% (n=44), follicular carcinoma 0.3% (n=1), medullary carcinoma 0.3% (n=1) and anaplastic carcinoma 0.3% (n=1). Multinomial regression analysis revealed that temporary hypocalcemia was associated with graves' disease (Odds ratio: 11.6), PTC (10.3), follicular adenoma (16.7) and thyroiditis (17.5), while permanent hypocalcemia was associated only with thyroiditis (3.2), each p<0.01.

**Conclusions:** Graves' disease, thyroiditis and malignancy increased the risk of temporary post-thyroidectomy hypocalcemia by many-fold. Subjects with thyroiditis had 3.2-fold increased likelihood for developing permanent hypocalcemia. Hence thyroiditis, a benign pathology warrants high threshold for surgery with meticulous intraoperative dissection and in-situ preservation of parathyroid glands.

**Keywords:** Post-thyroidectomy hypocalcemia, Permanent hypocalcemia, Thyroiditis, Graves' disease, Malignancy, Papillary thyroid carcinoma

## INTRODUCTION

Total thyroidectomy (TT) is the recommended procedure of choice for many thyroid diseases including thyroid cancer which is increasing across the globe.<sup>1-3</sup> With increasing incidence of thyroid diseases requiring surgery, TT is increasingly performed worldwide and an accompanying increase in the incidence of post-

thyroidectomy hypocalcemia (PH) is as well reported.<sup>4,5</sup> PH remains a concern after TT as life-threatening hypocalcemic complication tend to develop in the first or second postoperative day demanding repeated blood investigation, intravenous calcium therapy with or without vitamin D therapy, thereby prolonging the hospital stay and increasing the costs. PH is often temporary with a registered incidence of 1.2-40%.<sup>6</sup>

Permanent hypocalcemia persisting 6-months beyond surgery occurs in 0.2-10% of cases and may require life-long calcium supplementation.<sup>7</sup>

Hypoparathyroidism resulting from accidental removal or vascularity compromise of one or more parathyroid gland during surgery is the most commonly accepted cause of PH. However, permanent damage to 2 or more parathyroid glands with inadequate parathyroid reserve result in permanent hypoparathyroidism and consequently permanent hypocalcemia.

With turn of the century, there is changing trend in the epidemiology of thyroid diseases across the globe.<sup>1,8,9</sup> With iodine supplementation programme, there is decreasing incidence of iodine-deficient disorders including congenital hypothyroidism and endemic goitre. On the contrary, incidence of thyrotoxicosis, thyroiditis and thyroid cancer is increasing in iodine replete areas. The global incidence of thyroid cancer has tripled over the past decade, of which >90% is accounted by papillary thyroid carcinoma (PTC) histology, especially in affluent countries. Global epidemiological studies reveal that the incidence and prevalence of thyroid diseases are influenced by geographic location, environmental factors, socio-economic status, dietary habits and national screening program. Data from national cancer registry program of Indian council of medical research (ICMR) has revealed rising trend in thyroid cancer rate in the coastal districts of Kerala, in contrast to the very low prevalence in the sub-himalayan iodine-deficient endemic goitre belt of northern India. In the absence of adequately powered epidemiological data regarding the current incidence and prevalence of thyroid diseases across the country, there is a pressing need to determine the incidence pattern of various thyroid pathology, including thyroid cancer across iodine-sufficient eastern coastal districts of southern India.

Therefore, we conducted this prospective study with aim to determine the histopathologic pattern, age-and gender-distribution of thyroid diseases requiring surgery and correlated its effect on the development of transient and permanent postoperative hypocalcemia post-TT at large volume tertiary care Government General Hospital in iodine-sufficient Chennai in southern India.

## METHODS

Consecutive patients undergoing TT in the Department of Endocrine surgery, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-600003 from July 2017 to December 2019 were enrolled in the study. Institutional ethics committee approval obtained. Informed written consent obtained from all the individual participants. Age, sex, income, complete blood count, renal and liver biochemistries, thyroid-specific investigations including thyroid profile, thyroid auto-antibody, high frequency neck ultrasound and cytology findings were documented. Serum corrected-calcium and

intact parathormone was measured at baseline, 24-hour, 48-hour and 6-month post-TT using Roche automated analyzer eCobas6000 series, Switzerland.

Diagnosis of Graves' disease was based on clinical signs and symptoms of hyperthyroidism, suppressed thyroid stimulating hormone (TSH) and elevated thyroid hormones levels. Hashimoto's thyroiditis was diagnosed with serological elevation of anti-thyroglobulin and anti-thyroperoxidase antibody and cytology.

Cytology based on the Bethesda system for reporting thyroid cytopathology was considered diagnostic for benign thyroid diseases except follicular adenoma (FA) and malignant thyroid diseases except follicular thyroid carcinoma (FTC) which needs tissue diagnosis for demonstration of capsular and vascular invasion. The final diagnosis was confirmed with histopathological examination (HPE) of thyroidectomy specimen. Subjects who are surgical candidates for TT were included in the study. Indication for surgery was presence of any of the following: 1) large volume goitre with compression symptoms 2) cytology suspicious for malignancy or indeterminate cytology 3) retrosternal extension 4) Grave's disease or toxic multinodular goitre resistant to anti-thyroid therapy and 5) patient's preference for surgery for cosmetic and logistic reasons. Subjects with intentional parathyroidectomy, revision surgery, concurrent cervical lymphadenectomy, those with chronic medical conditions/medications interfering with calcium metabolism and those unwilling for enrollment were excluded from the study.

Preoperatively, subjects with hyperthyroidism received antithyroid drug, tab. carbimazole and hypothyroid patients (subset of thyroiditis) received tab. thyroxine sodium prior to surgery. On achieving euthyroidism, classic TT was performed adhering in-house standards by same surgical team identifying and preserving all the parathyroid glands and laryngeal nerves. Number of parathyroid glands preserved and auto-transplanted were noted.

Postoperatively, subjects were monitored for signs and symptoms of hypocalcemia including perioral and acral numbness, carpopedal spasm, arrhythmia, seizures, laryngospasm, bronchospasm and Troussseau's sign. Transient hypocalcemia was defined as serum corrected-calcium <8.4 mg/dL and/or symptoms and signs of hypocalcemia less than 6-months post-TT. Permanent hypocalcemia was defined as the requirement for calcium  $\pm$  calcitriol to remain eucalcemic at 6-months or more after TT. Hypoparathyroidism was defined as iPTH <10 pg/mL. Hypocalcemia was treated with oral calcium carbonate 0.5-3 g/day  $\pm$  calcitriol (active vitamin D) 0.25-1 mcg/day in divided doses. Intravenous 10% calcium gluconate (9.3 mg elemental calcium per ml) administered as initial IV bolus 1000 mg and subsequent

continuous IV infusion at 5-10 mg/kg/hour depending on acuity and severity of hypocalcemia.

### Statistical analysis

Statistical analysis was performed with SPSS statistics, version 20.0. Armonk, NY, IBM Corp. Categorical data was expressed as frequencies (n) and percentage and continuous data as mean±standard deviation. Chi-square test compared categorical variables. Multinomial logistic regression test was fitted to analyze the determinants of dependent variable. Results were expressed as odd's ratio (OR) and 95% Confidence Interval (CI). P value< 0.05 was considered statistically significant.

## RESULTS

Total of 340 prospectively studied subjects who underwent TT, 328 subjects including 65 male and 263 females with mean age of 35.5 years were eligible for analysis. The mean follow-up was 17.1±6.0 months. Subjects with concurrent neck dissection or other comprehensive procedures, revision surgery, intentional parathyroidectomy and subjects with incomplete

corrected-calcium and iPTH values or lost in the follow-up were excluded.

Temporary and permanent hypocalcemia was seen in 33.4% (n=109) and 7.6% (n=26). HPE of formalin-fixed paraffin embedded blocks of surgical specimen was reported in accordance with WHO classification of endocrine tumors. Histopathology comprised of colloid goitre 33.2% (n=109), follicular adenoma 1.8% (n=6), Hashimoto's thyroiditis 13.4% (n=44), chronic lymphocytic thyroiditis 3.4% (n=11), Graves' disease 14% (n=46), adenomatous hyperplasia 19.8% (n=65), papillary thyroid carcinoma (PTC) 13.4% (n=44), FTC 0.3% (n=1), medullary thyroid carcinoma (MTC) 0.3% (n=1) and anaplastic thyroid carcinoma (ATC) 0.3% (n=1). The age, gender-distribution and percent incidence of temporary and permanent hypocalcemia in each histological subtype was summarized (Table 1 and 2). Thirteen patients had parathyroid auto transplantation into ipsilateral sternocleidomastoid muscle including 5 cases of Graves' disease, 4 cases of thyroiditis, 3 cases of PTC and one-subject with adenomatous hyperplasia. Parathyroid gland was identified in thyroidectomy specimen of two cases of Hashimoto's thyroiditis and one-case of Graves' disease.

**Table 1: Age and gender distribution of subjects, percent incidence of temporary and permanent hypocalcemia under each histological subtype.**

Histology	Total	Age ≤45: >45 years	Male: Female	Temporary hypocalcemia	Permanent hypocalcemia
	N (%)			N (%)	N (%)
<b>Anaplastic carcinoma</b>	1 (0.3)	1:0	1:0	1 (0.9)	0
<b>Medullary carcinoma</b>	1 (0.3)	0:1	0:1	1 (0.9)	0
<b>Follicular carcinoma</b>	1 (0.3)	1:0	0:1	1 (0.9)	0
<b>Papillary carcinoma</b>	44 (13.4)	33:11	8:36	25 (22.9)	6 (23.1)
<b>Adenomatous hyperplasia</b>	65 (19.8)	46:19	10:55	5 (4.6)	3 (11.5)
<b>Graves' disease</b>	46 (14)	27:19	12:34	25 (22.9)	4 (15.3)
<b>Thyroiditis</b>	55 (16.8)	38:17	15:40	36 (33)	10 (38.4)
<b>Follicular adenoma</b>	6 (1.8)	4:2	1:5	4 (3.7)	0
<b>Colloid goitre</b>	109 (33.2)	72:37	18:91	11 (10.1)	3 (11.5)
<b>Total</b>	328 (100)	222:106	65:263	109 (100)	26 (100)

**Table 2: Age distribution across each histological subtype.**

Variables	Age group in years						Total
	11-20	21-30	31-40	41-50	51-60	>61	
<b>Anaplastic carcinoma</b>	Count	0	0	1	0	0	1
	% of total	0.0	0.0	0.3	0.0	0.0	0.3
<b>Follicular carcinoma</b>	Count	0	0	0	1	0	1
	% of total	0.0	0.0	0.0	0.3	0.0	0.3
<b>Medullary carcinoma</b>	Count	0	0	1	0	0	1
	% of total	0.0	0.0	0.3	0.0	0.0	0.3
<b>Papillary carcinoma</b>	Count	3	12	17	8	1	44
	% of total	0.9	3.7	5.2	2.4	0.3	13.4
<b>Adenomatous hyperplasia</b>	Count	3	14	24	15	5	65
	% of total	0.9	4.3	7.3	4.6	1.5	19.8

Continued.

Variables	Age group in years						Total
	11-20	21-30	31-40	41-50	51-60	>61	
Graves' disease	Count	2	11	11	14	6	2 46
	% of total	0.6	3.4	3.4	4.3	1.8	0.6 14.0
Thyroiditis	Count	3	12	19	10	10	1 55
	% of total	0.9	3.7	5.8	3.0	3.0	0.3 16.8
Follicular adenoma	Count	0	1	1	3	0	1 6
	% of total	0.0	0.3	0.3	0.9	0.0	0.3 1.8
Colloid	Count	6	27	29	31	13	3 109
	% of total	1.8	8.2	8.8	9.5	4.0	0.9 33.2
Total	Count	17	77	103	82	35	14 328
	% of total	5.2	23.5	31.4	25.0	10.7	4.3 100.0

**Table 3: Multinomial logistic regression model was fitted for the analysis of determinants of transient and permanent hypocalcemia.**

Histology	Transient hypocalcemia			Permanent hypocalcemia			Odds Ratio (95% confidence interval)
	B (co-efficient)	P value	Odds Ratio (95% confidence interval)	B (co-efficient)	P value	Odds Ratio (95% confidence interval)	
Age	0.005	0.686	1.0 (0.9-1.0)	0.008	0.613		
Gender	-0.3	0.385	0.7 (0.4-1.5)	-0.743	0.254		
48-hour parathormone	0.7	0.021	2.0 (1.1-3.6)	1.023	0.016	2.7 (1.2-6.4)	
Anaplastic carcinoma	21.2	-	-	-	-		
Medullary carcinoma	20.1	-	-	-	-		
Follicular carcinoma	20.9	-	-	-	-		
Papillary carcinoma	2.3	< 0.001	10.3 (4.3-24.9)	0.589	0.330		
Adenomatous hyperplasia	-0.4	0.469	0.7 (0.2-2.0)	-0.508	0.478		
Graves' disease	2.5	< 0.001	11.6 (4.8-27.7)	0.379	0.569		
Thyroiditis	2.9	< 0.001	17.5 (7.4-41.1)	1.154	0.032	3.2 (1.1-9.1)	
Follicular adenoma	2.8	0.003	16.7 (2.6-106.2)	-15.901	0.997		
Colloid goitre	redundant						

Serum levels of calcium and iPTH was preoperatively  $9.1 \pm 0.9$  mg/dl and  $32.1 \pm 22.3$  pg/ml; at 48-hours post-TT,  $8.2 \pm 1.1$  mg/dl and  $17.7 \pm 21.8$  pg/mL and; 6-month post-TT,  $9.1 \pm 0.8$  mg/dl and  $33.3 \pm 24.1$  pg/ml respectively. There was statistically significant difference in the incidence pattern of post-thyroidectomy hypocalcemia across histological subtypes ( $p < 0.001$ ) but no difference with respect to age ( $p = 0.614$ ) and gender-distribution ( $p = 0.320$ ). Hashimoto's thyroiditis and lymphocytic thyroiditis was considered together as thyroiditis for analysis purpose.

In age-and gender-adjusted multinomial analysis (Table 3), the determinants of temporary hypocalcemia were Graves' disease (OR: 11.6), PTC (OR: 10.3), follicular adenoma (OR: 16.7), thyroiditis (OR: 17.5) and 48-hour iPTH (OR: 2), while permanent hypocalcemia was associated with thyroiditis (3.2) histological subtype alone and 48-hour iPTH (OR: 2.8), each  $p < 0.01$ .

## DISCUSSION

With rising trend of thyroid cancer, thyroiditis and thyrotoxicosis, there is a pressing need to determine the incidence pattern of thyroid diseases requiring surgery, particularly in iodine-sufficient areas. Moreover, increasing incidence of postoperative hypocalcemia is reported with the technique of total thyroidectomy, the recommended procedure for thyroid cancer and many benign diseases. Our study addressed these two issues. First, the study revealed the incidence pattern, age-and gender-distribution across each histological subtype among of subjects undergoing TT in coastal district of South India. Second, it correlated the development of both temporary and permanent hypocalcemia across each histopathological subtype after TT.

The present study demonstrated that colloid goitre was the most common histological subtype constituting 33.2% followed by adenomatous hyperplasia 19.8%,

Graves' disease 14%, PTC 13.4%, Hashimoto's thyroiditis 13.4%, lymphocytic thyroiditis 3.4%, follicular adenoma 1.8%, FTC 0.3%, MTC 0.3% and ATC 0.3%. Thyroid disease had preponderance for female sex and highest prevalence (31.4%) was seen in the 4th decade of life. Papillary thyroid carcinoma was the most common cancer histology accounting for 93.6% of malignancy with a female preponderance (85.7%) and majority of cases were below 45 years of age. Our findings were consistent with published reports.<sup>10-12</sup> The highest incidence of temporary hypocalcemia post-TT was seen in Thyroiditis (33%) followed by PTC and Graves' disease, each constituting 22.9%.

Multinomial logistic regression analysis revealed that patients with Hashimoto's thyroiditis was 17.5 times more likely to develop temporary hypocalcemia compared to subjects with colloid goitre undergoing TT. PTC and Graves' disease were associated with 10.3 and 11.6-times increased likelihood for temporary hypocalcemia respectively. In contrast to previous reports, advanced age and female gender was not associated with increased risk for temporary PH. Subjects with transient hypoparathyroidism had 2-fold increased odds of developing temporary PH.

Interestingly, follicular adenoma a benign histology was associated with 16.7-odds of developing temporary hypocalcemia. All the of six-cases of follicular adenoma observed in this study was initially diagnosed as Bethesda category i.e. suspicious of follicular neoplasm on cytology. It is probable that large volume goitre and increased vascularity incidentally observed in this subset could have confounded the impact on temporary PH.

The present study revealed that permanent hypocalcemia was highest in subjects with thyroiditis (38.4%) followed by PTC (23.1%) and Graves' disease (15.3%). However, on multinomial logistic regression analysis, thyroiditis (OR: 3.2) and permanent hypoparathyroidism (OR: 2.8) were the independent risk factors for permanent hypocalcemia after TT. PTC and Graves' disease was associated with increased incidence of permanent hypocalcemia, but failed to reach significance on regression analysis. Thus, routine intraoperative identification and preservation of parathyroid glands increased the risk of temporary hypocalcemia but improved the long-term rates of permanent hypocalcemia.

The study demonstrated coexistence of Hashimoto's thyroiditis in some of the patients with nodular hyperplasia, adenomatous hyperplasia as well as PTC. The stepwise progression of nodular hyperplasia through adenomatous hyperplasia to full-fledged PTC in subjects with co-existing Hashimoto's thyroiditis and unravelling of molecular pathways involved in this multi-step carcinogenesis is an area of future research.<sup>13,14</sup>

Recent evidences have shown that there is a positive correlation between Hashimoto's thyroiditis and PTC, which is consistent with our observation. However, large prospective studies are needed to elucidate the causal association between thyroiditis and PTC.<sup>15-17</sup>

Thus, thyroiditis, a benign histology impacted both short-term and long-term rates of hypocalcemia after TT. Therefore, we recommend that primary approach for thyroiditis shall be medical treatment. The initial thyrotoxic phase of thyroiditis need treatment with beta-adrenergic blockers and non-steroidal anti-inflammatory drugs for symptomatic relief. Later, supplementary doses of levothyroxine may be needed for hypothyroidism. Thyroiditis subjects harboring high risk for malignancy including family history of cancer, recent rapid growth of goitre, suspicious features for malignancy on neck-ultrasound or cytology should be judiciously selected for surgery.

### Limitations

The study has not included lobectomy, hemithyroidectomy, thyroidectomy with neck dissection and hence there could be underestimation of the incidence pattern of thyroid diseases requiring surgery. The study focused only on subjects undergoing TT in order to determine the true incidence of PTC, as microcarcinoma could be missed in lesser resection procedures. Furthermore, the incidence of postoperative hypocalcemia was evaluated for the uniform technique of TT, which is the minimum procedure of choice for malignancy, as the occurrence of PH varies with extent of thyroidectomy.

### CONCLUSION

Colloid goitre was the most common histopathology accounting for 33.2% of patients undergoing TT. Papillary thyroid carcinoma was the most common cancer histological subtype with an incidence of 13.4% and accounted for 93.6% of thyroid malignancy. Graves' disease and malignancy increased the risk of temporary hypocalcemia several-fold post-TT. Hashimoto's/ Chronic lymphocytic thyroiditis, a benign pathology affected both short-term and long-term rates of hypocalcemia after TT and hence warrants high threshold for surgery with meticulous intraoperative dissection and in-situ preservation of parathyroid glands.

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